STRESS ECHOCARDIOGRAPHY

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Stress echocardiografie

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To my parents, who showed me the way.

To my beloved Matilde and our two wonderful boys Luca and Francesco who are my happiness.

CONTENTS

PART ONE

INTRODUCTION

CHAPTER 1.

INTRODUCTION

Non-invasive diagnosis and assessment of coronary artery disease represent a major challenge for cardiologists. Currently, provocative testing coupled with techniques which reveal myocardial ischaemia are increasingly employed. The ideal test should be safe, practical, cheap, with a very high accuracy. Electrocardiography and nuclear imaging have been extensively used in conjunction with stress testing, and their advantages and limitations are now well documented (1-7).

Stress echocardiography is a relatively new technique, based on the detection of new wall motion abnormalities as a marker of myocardial ischaemia by ultrasonographic techniques. There is a growing interest in stress echocardiography, which offers advantages over the established methods and represents an alternative to more sophisticated techniques.

RATIONALE OF STRESS ECHOCARDIOGRAPHY

The basis of stress echocardiography relies on the metabolic pathways of the myocardial cell. At rest, 60% of the high-energy phosphate derived from the metabolism of the cell is utilized for contractility, 15% for relaxation, 5% for electrical activity. The remaining 20% is necessary for maintaining cell integrity (8). These so called "wear and repair" processes represent a metabolic priority for the cell. Thus, during ischaemia, when the support of phosphates is decreased, the first activity to be reduced is contractility. Regional dysfunction is directely related to reduction of regional blood flow, and represents a sensitive "semiquantitative" index of regional ischaemia (9). The relationship between subendocardial flow and systolic wall thickening is represented in Table I.

TABLE I

reduction of subendocardial blood flow	reduction of myocardial thickening
20%	15-20%
50%	40%
80%	100%

Reduction of subendocardial blood flow >80% generally extends to subepicardium, and results in dyskinesis. Regional myocardial dysfunction can be detected by two-dimensional echocardiography.

ULTRASONIC MARKERS OF MYOCARDIAL ISCHAEMIA

The ultrasonic markers of regional myocardial ischaemia are represented in Table II.

TABLE II

WALL	REGIONAL DYSSYNERGY	Hypokinesis	= reduction of systolic inward motion of LV wall
		Akinesis	= absence of systolic motion of LV wall
		Dyskinesis	= paradoxical systolic motion of LV wall
	SYSTOLIC WALL THICKENING IN PERCENT		
CAVITY	LEFT VENTRICULAR DILATION		
DOPPLER	AORTIC VELOCITY		Aortic peak flow velocity Aortic flow velocity integral
	MITRAL VELOCITY		E/A ratio
	COLOR FLOW		Acute mitral regurgitation

The cardinal signs of transient myocardial ischaemia involve left ventricular wall. The three grades of impaired wall motion represent an arbitrary classification, based on subjective semi-quantitative analysis of images. In this respect, intraobserver and interobserver variability should be minimal to maintain acceptable clinical reliability of the diagnosis of hypokinesis. Theoretically, decreased systolic wall thickening is a more sensitive sign of myocardial ischaemia than wall motion. Regional wall motion can be affected by other non-ischaemic factors, such as left bundle branch block, volume overload, post-operative paradoxical septal motion, tethering by adjacent segments. Moreover, systolic wall thickening is an active process and represents the true expression of contractility. Generally, both wall motion and systolic thickening are evaluated when echocardiograms are analysed for the assessment of transient myocardial ischaemia.

Transient left ventricular cavity dilation is an ancillary sign of ischaemia, and often accompanies impairment of wall dynamics (10). Sometimes, an increase in systolic left ventricular dimension is the first echocardiographic sign that becomes evident during ischaemia.

Doppler signs of systolic or diastolic dysfunction are less sensitive indicators of ischaemia; rather, they point to the extent of myocardial ischaemia (11). Theoretically, diastolic dysfunction precedes systolic dysfunction, but the clinical application of indices of diastolic function has not been found superior to wall motion analysis from two-dimensional echocardiogram (12).

STRESS ECHOCARDIOGRAPHY VS NUCLEAR CARDIOLOGY

Radionuclide stress techniques have been extensively applied for both the diagnosis and evaluation of myocardial ischaemia due to coronary artery disease. Both radionuclide angiography and perfusion scintigraphy have been demonstrated to have good diagnostic accuracy in a large series of studies (13-16). Thus, stress echocardiography has been compared to coronary arteriography (the anatomical reference method) and/or nuclear techniques (the reference method for the diagnosis of myocardial ischaemia). However, from a pathophysiological point of view, some important differences between the two techniques exist. First, the end-points of stress echocardiography and perfusion myocardial scintigraphy are different. Positivity of perfusion scintigraphy relies on the detection of a relative difference in perfusion between myocardial segments supplied by different arteries (6). Therefore, the presence of myocardial ischaemia is not essential for a positive test. On the contrary, ischaemia is the diagnostic end-point for stress echocardiography. This important issue can explain the lower specificity of perfusion scintigraphy when compared to stress echocardiography (17).

Another important difference with practical implications is represented by the recognition of the time of onset of myocardial ischaemia. Myocardial scintigraphy is performed without on-line assessment of imaging, while with stress echocardiography wall motion can be monitored, which allows identification of the time of onset of ischaemia (18). The test can be stopped when new or worsened wall motion abnormalities are observed. Thus, stress echocardiography is potentially safer than perfusion scintigraphy, where monitoring is achieved by elusive markers of ischaemia such as chest pain and ECG changes. Finally, the information derived from the time of onset of ischaemia is relevant for prognostication of patients (19).

STRESS MODALITIES

Many different stress methods have been used in conjunction with echocardiography, including exercise (bicycle or treadmill, with echocardiographic recording at peak or immediately post-exercise) (20), atrial pacing (intracavity and more recently transesophageal) (21), and pharmacological agents (dipyridamole, adenosine, dobutamine, arbutamine) (22). Transesophageal atrial pacing and recording have been successfully applied (23), but it is unlikely that this "semi-invasive" approach will replace precordial echocardiography, at least for routine clinical practice.

Exercise echocardiography

Dynamic exercise is the most physiological type of stress and the most popular test for eliciting myocardial ischaemia. Physical activity is the usual way by which ischaemia is provoked during daily life, and a diagnostic test that reproduces these events will provide the most clinically relevant information. Different modalities of exercise can be adapted to two-dimensional echocardiography. In Europe, bicycle exercise is by far the most common type of dynamic stress test, and is usually performed in the upright position. Bicycle exercise offers some advantages over treadmill when echocardiographic imaging is coupled.

TABLE III

COMPARISON OF BICYCLE AND TREADMILL EXERCISE ECHOCARDIOGRAPHY.

ECHO IMAGING	BICYCLE	TREADMILL
Quality	++	-
Throughout exercise	yes	no
Peak exercise	yes	no
Post-exercise	yes	yes

Generally, echocardiographic images are recorded at rest and immediately after exercise has been terminated. Parasternal long- and short-axis, and apical four- and two-chamber views are usually recorded, both at rest and post-exercise, in the same left lateral position. Some disadvantages of this method shoul be outlined:

1) although rest images are usually of good quality, deterioration immediately after stress occurs. This is mainly due to excessive breathing causing respiratory artifacts and making the heart moving in and out the examining plane;
2) theoretically, myocardial ischaemia can be short lasting. In the presence of milder degrees of ischaemia, wall motion abnormalities may reverse quickly after termination of exercise. Thus, the real extent and severity of ischaemia may be underestimated, limiting the potential role of post-exercise echocardiography as a prognostic tool;
3) with this "two-step" protocol, only rest and post-exercise images are recorded. Myocardial wall motion and cardiac function are not monitored throughout the entire study, and the ischaemic threshold (i.e., the minimum workload at which wall motion abnormalities begin to occur) cannot be evaluated.

The use of two-dimensional echocardiography in conjunction with stress testing was first reported in 1979 (24). However, despite promising results and initial enthusiasm (25-31), some technical problems hampered its widespread application. Successful imaging was possible in only 70-80% of patients, the overall image quality was suboptimal, the images at peak exercise are very difficult to analyse, and the comparison between rest and stress images was made going "back and forward" on the videotape in order to detect subtle changes in wall motion. Reference images at rest were kept in mind and compared with those obtained at stress. Furthermore, peak images were often represented by isolated cardiac cycles interrupted by respiratory artifacts. In this way, analysis was difficult and tedious, thus hampering routine application. These drawbacks and the concomitant emergence of radionuclide techniques limited the widespread use of exercise echocardiography.

Two factors renewed the interest in exercise echocardiography in the mid 1980's. First, technological advances in ultrasound equipment improved the image quality, and second, digital processing techniques were introduced and combined with echocardiographic imaging. These technical innovations increased the availability and acceptance of the technique significantly.

Supine bicycle ergometry is another stress modality. There are some differences between upright and supine posture during bicycle exercise (Table IV). A higher workload is attained in the upright position, with a greater increase in left ventricular systolic function and arterial pressure.

TABLE IV

HAEMODYNAMIC DIFFERENCES BETWEEN UPRIGHT AND SUPINE BICYCLE ERGOMETRY.

	UPRIGHT	SUPINE
HEART RATE	+++	++
BLOOD PRESSURE	+++	++
WORKLOAD	+++	++
STROKE VOLUME	++	++
CARDIAC OUTPUT	+++	++
LVED PRESSURE	++	+++
LVED VOLUME	++	+++
WALL STRESS	++	+++
LV CONTRACTILITY	+++	++

From a practical point of view, these conclusions can be summarized:

1) Echocardiographic images can be combined with all types of dynamic exercise;
2) whatever exercise modality used, digital recording and cine-loop display of echocardiographic images are necessary for interpretation of the test;
3) treadmill stress test only allows for echocardiographic imaging at rest and immediately after interrupting exercise. Recording at peak stress is possible with bicycle ergometry;
4) supine bicycle echocardiography (32) offers the advantage that all views can be recorded, while in the upright position it is limited to the apical and subcostal wiews;
5) the technique is highly dependent on the ability of the operator to record good images. When a post-exercise protocol is used, the time interval between cessation of exercise and recording is extremely important. This is the major limiting factor for the interpretation of the results of the test.

The latter point and the fact that at least 30% of patients referred for the assessment of myocardial ischaemia are unable to perform an adequate exercise led to the search for "alternative" stress methods.

Atrial pacing stress test

The difficulties in performing and the artifacts interfering with the interpretation of exercise stress echocardiograms stimulated investigators to look for alternative stress methods. There is experimental evidence supporting the concept that during atrial pacing there is a redistribution of flow (33), resulting in a reduction of subendocardial/subepicardial blood flow in the presence of a coronary stenosis (34). In the past years, the feasibility of transesophageal atrial pacing was limited by excessive discomfort for the patient. Recently, the improvement in pacing electrodes and technology allowed to lower the current intensity, and as a result transesophageal atrial pacing is now better tolerated.

The protocol for the test is based on atrial pacing started at 110 b/min, with increments every two minutes by 10 b/min, until a heart rate of 150 b/min is achieved. This stage is then maintained for 5 minutes, if no wall motion abnormalities are induced. Premedication with atropine (0.02 mg/Kg iv) should be used in patients with a low Wenckebach point (21).

Only few investigators have assessed the feasibility, the safety, and the diagnostic utility of transesophageal atrial pacing in conjunction with precordial echocardiography for the diagnosis of coronary artery disease (35). More recently, Lambertz et al (23) combined the use of simultaneous transesophageal pacing and transesophageal echocardiography. Despite excellent initial results, it remains to be proven whether this approach is superior to the usual transthoracic approach in clinical practice. It is likely that this method will be confined to patients with poor precordial echocardiograms or for research purposes, e.g. when quantitative data are requested.

Cold pressor test

Sometimes, the exposure to cold may worsen the anginal pain in patients with coronary artery disease. The mechanisms involved are mostly related to an increase in peripheral vascular resistance and possibly in the coronary arteries. The increase in blood pressure results in an increase in afterload which is one of the major determinants of myocardial oxygen consumption. However, only two studies have been reported in the literature on its application combined with ultrasonic imaging (36,37) and a low diagnostic accuracy was found. Thus, the value of cold pressor test as a provocative test in conjunction with two-dimensional echocardiography appears to be limited.

Handgrip

Handgrip is an alternative stress modality in patients unable to perform exercise. The sudden rise in blood pressure due to the isometric exercise increases myocardial oxygen demand. The test is ideal in combination with two-dimensional echocardiography as the lack of motion and hyperventilation does not limit image quality. However, heart rate and cardiac output are not significantly increased. Data on two-dimensional echocardiography during isometric exercise are limited (38,39). Ideally, the test may be combined with other pharmacological stress agents, as dipyridamole or adenosine, to further increase the potential for inducing ischaemia via a different mechanism.

Pharmacological stress

Although exercise is the most physiological method to achieve a maximal level of stress, some patients are unable to perform conventional exercise stress testing adequately. Such limitation can be due to lung disease, peripheral vascular disease, central nervous system disorders, deconditioning, or orthopedic problems. Moreover, technical problems related to echocardiographic monitoring during dynamic exercise stimulated the use of pharmacological stress agents.

Pharmacological stresses are ideal partners of imaging methods in general and of echocardiography in particular. The patient maintains the same left lateral decubitus throughout the test, avoiding hyperventilation, and the heart can be adequately imaged from different windows and in different views, in search for new wall motion abnormalities. Moreover, pharmacological stress allows continuous monitoring and ischaemia can be detected from its onset. The ischaemic threshold can thus be evaluated and the test safely performed.

a. Dipyridamole

Dipyridamole was the first pharmacological agent used for stress echocardiography (40). The physiological basis for inducing myocardial ischaemia and its mechanisms of action have been extensively reviewed (41). The vasodilator effect of dipyridamole is related to the increased plasma level of endogenous adenosine. Dipyridamole acts by inhibiting adenosine-deaminase (the enzyme that converts adenosine into inosine) and by preventing adenosine re-uptake into myocardium. The haemodynamic mechanism responsible for dipyridamole-induced ischaemia is related to a decrease in oxygen supply to a region supplied by a critical coronary artery stenosis by a "steal effect".

After the initial experience with a cumulative dose of 0.56 mg/Kg over 4 minutes, Picano and coworkers reported acceptable values of sensitivity and a very high specificity for the diagnosis of coronary artery disease using a higher dose (0.84 mg/Kg over 10 minutes) (42). Nowadays, this is the protocol used for dipyridamole stress echocardiography. Aminophylline, which blocks the adenosine receptors, is the antidote of dipyridamole. It is administered intravenously (70-240 mg) for rapid reversal of dipyridamole-induced myocardial ischaemia and for treatment of side effects.

The test has been applied for detecting the presence of multiple vessel disease in patients after a first myocardial infarction (43), in the pre- and post- angioplasty evaluation of patients mostly with one-vessel disease (44,45), for prognostication of patients with chest pain or with previous myocardial infarction (46). Finally, the multicenter Echo Persantin International Cooperative Study (EPIC) provided a large amount of data on the safety, the diagnostic accuracy, and the prognostic value of dipyridamole echocardiographic test (47,48).

b. Adenosine

Based on the mechanism of action of dipyridamole, some investigators proposed the use of the "second messenger" adenosine to achieve a vasodilatory effect (49). The main feature of adenosine is its extremely short half-life, but the depression of sino-atrial or atrio-ventricular node function can result in bradyarrhythmias. The nature of the side effects of adenosine are similar to those of dipyridamole, and aminophylline is used as antagonist. From a theoretical point of view, the clinical application and the results of adenosine as a stress agent should be similar to those obtained with dipyridamole. However, until now few data are available on adenosine stress echocardiography (50), and more data are requested to assess the safety and the diagnostic accuracy of this test.

c. Arbutamine

Arbutamine is a new catecholamine producing increases in heart rate and myocardial contractility. Arbutamine is administered intravenously through a computerized delivery system designed to monitor the patient's heart rate and blood pressure. In this way, the amount of drug delivered is based on the heart response to the drug. There are only preliminary results on the potential role of this drug as a stress agent for the diagnosis of coronary artery disease (51).

d. Dobutamine

Dobutamine is a synthetic catecholamine, which has the property to stimulate beta1, beta2, and alfa1-adrenoceptors in the cardiovascular system. The apparent selective inotropic effect of dobutamine is due to the alfa1-adrenoceptors located in the heart (52). The drug increases also heart rate and, to a lesser degree, blood pressure, causing an increase in myocardial oxygen demand. Direct beta2-adrenoceptor-mediated activity in the peripheral vasculature induces substantial vasodilation. Its mechanism is more "physiological" than dipyridamole, and is similar to exercise stress testing (exercise simulator).

Different protocols have been used for dobutamine stress echocardiography. The following aspects are of importance:

1) low-dose infusion (5-10 mcg/Kg/min) elicits a pure inotropic response with mild increase in myocardial oxygen demand, and is used to evaluate viability of the myocardium;
2) a 3-minute intervals for increments in dosage of 10 mcg/Kg/min up to 40 mcg/Kg/min represent a compromise between pharmacokinetic properties of dobutamine and feasibility of the test;
3) the addition of atropine on top of dobutamine infusion increases the sensitivity of the test, particularly in patients on beta-blocker therapy, without loss of specificity (53);
4) intravenous beta-blocker is the antidote to reverse dobutamine and atropine side effects.

The use of high-dose dobutamine as a stress agent was not very widespread until recently. However, increasing evidence is accumulating that the test is accurate and reproducible for the diagnosis of coronary artery disease and very suitable for use in conjunction with echocardiographic monitoring in many different clinical settings (54).

PRACTICAL ASPECTS OF STRESS ECHOCARDIOGRAPHY

1) Criteria of a positive test

The identification of ischaemia is based on the comparison between rest and images during stress. Thus, the pattern of contractility at rest clearly influences the response of the left ventricle to stress. Two clinical conditions should be considered:

a. Normal wall motion at rest..

In this situation, a stress-induced wall motion abnormality can be considered as a marker of myocardial ischaemia. The type of induced dyssynergy (hypokinesis, akinesis, or dyskinesis) identifies different grades of severity of ischaemia (see Table II).

In general, identification of regional akinesis or dyskinesis is easy. Less clear is the definition of hypokinesis. There is no clear transition between normal contraction and hypokinesis, and the final assessment relies on subjective evaluation. Moreover, in most cases, hypokinesis of one region is defined upon a relative hyperkinesis in other segments, rather than absolute deterioration of wall motion as compared to resting wall motion. This is particularly true when inotropic stress modalities are used, such as exercise or dobutamine. Furthermore, in patients performing stress echocardiography on antianginal medication (expecially beta-blockers), the "normal" response to stress is unpredictable; thus, the relative comparison of wall motion of different segments becomes less reliable.

b. Abnormal wall motion at rest.

b1. Hypokinetic segments.

The diagnosis of stress-induced ischaemia in segments which are already hypokinetic at rest is probably the most difficult aspect of stress echocardiography for several reasons. First, the term hypokinesis includes a continuous spectrum of a decrease of wall motion, from minor degrees to severe impairment. Secondly, the normal response of a hypokinetic segment to exercise, inotropic stimulation, and also vasodilatory agents, should be an increase in contractility, at least during the first stage of the test, and before myocardial ischaemia develops at a higher stress load. Thus, how should we interpret the absence of this improvement or the return to hypokinesis after a transient improvement? Clearly, a deterioration of wall motion (e.g., from hypokinesis to akinesis or dyskinesis) is considered as indicative of the presence of myocardial ischaemia.

b2. Akinetic segments.

Akinetic segments are generally not scored for the presence of residual myocardial ischaemia. A worsening from akinesis to dyskinesis can be due to increased ventricular loading conditions rather than true ischaemia, expecially during exercise or dobutamine stress test. However, there is both experimental and clinical evidence that akinetic myocardium can be viable but ischaemic (55), with an improvement of wall motion at early stages of exercise (or at low-dose of dobutamine or even at low-dose of dipyridamole infusion) and later return to akinesis. The potential advantages of this "integrated" evaluation of stress echocardiography remain to be studied.

Although the visual analysis of left ventricular wall motion depends on the complex spatial integration performed by human eyes throughout the entire stress test, in the studies of this thesis the following criteria for a positive test result have been used:

*normal wall motion at rest:

-development of any dyssynergy (hypokinesis, akinesis, dyskinesis) during stress;

*abnormal wall motion at rest:

-hypokinesis: worsening of contractility between rest and peak images;
-akinesis, dyskinesis: not analysable.

2. Criteria for the interruption of a pharmacological stress test

a. The left ventricular wall is monitored by echocardiogram during pharmacological stress test; thus, any stress-induced wall motion abnormality identifies the presence of myocardial ischaemia and represents the most reliable end-point and the standard criterium for terminating the test. In this way, safety of pharmacological stress echocardiography has been assured and proven in large series of patients (47). However, the interruption of the test when the first wall motion abnormality occurs may limit the potential value for the identification of all the diseased vessels, including stenoses of lesser degree than the culprit lesion. The balance between a complete evaluation of myocardial ischaemia and the safety of the test when the first new wall motion abnormality is not used as an end-point has not yet been determined and represents an area of future research.

b. The test is generally terminated when ST segment depression occurs. However, there is no agreement on the degree of ST segment depression which should be considered for discontinuation of the test. As wall motion abnormalities usually occur before ECG changes, reasons for terminating the test on the basis of ST changes are very rare.

c. Chest pain, particularly if severe and of anginal type, is always a reason for the termination of a stress test, even in the absence of new wall motion abnormalities.

d. Age-predicted maximal heart rate is an end-point of a dobutamine stress test, and represented by far the most frequent reason of interruption of infusion in a large series of patients at Thoraxcenter (56).

e. Severe side effects: chills, life-threatening arrhythmias, and dyspnea with dobutamine; and bronchospasm, bradyarrhythmias, headache, dizziness, nausea with dipyridamole may occur, but rarely require termination of pharmacological stress test.

f. Hypotension may occur during dobutamine infusion. Different criteria for hypotension has been used and its frequency varies between 11 and 20%. In the first studies on dobutamine stress echocardiography, a drop in systolic blood pressure of >20 mmHg was considered indicative of global myocardial dysfunction (as with exercise testing), and thus a sign for interrupting the test. However, no correlation was found between new wall motion abnormalities and the occurrence of hypotension during the test (57,58). The most likely mechanism for hypotension is a dynamic left ventricular outflow obstruction (59).

3. Technological development of stress echocardiography (60)

The application of digital recording techniques to stress echocardiography has facilitated both the performance and analysis of the tests. Digital frame grabbing systems permit to capture a series of frames of a single cardiac cycle, selected on the basis of its high quality, either off-line or on-line. These frames are usually eight, with a 50 msec interval starting from the R wave of electrocardiogram. Thus, a period of 350 msec is explored, representing the systolic phase for a wide range of heart rates. Once digitized, the images can be played in an endless-loop sequence and represented in a single-, dual-, or quad-screen format. Since only a single cardiac cycle is needed to create the cine-loop sequence, digital techniques have significantly reduced the image acquisition time. This is particularly important for immediate post-exercise imaging, where respiratory artifacts deteriorate image quality, and recording time must be minimal in order to get adequate information before subtle wall motion abnormalities may resolve.

In stress echocardiography, digital technology provides the opportunity to store standard views at rest and to capture all the corresponding post-exercise images. Then, selected pre- and post-exercise cine-loops are re-mixed and represented on one or two quad-screen format. By convention, rest images are displayed to the left of post-exercise images to allow immediate comparison of side-by-side rest/stress studies. Moreover, the continuous cine-loop display allows an unlimited time for review and facilitates a frame-by-frame analysis. This improves the ability to detect subtle wall motion abnormalities. With digital techniques, storage, retrieval and display of stress echocardiograms are favorably affected. An entire stress study can be stored on a simple hard-disk, floppy-disk or optical-disk, and serial studies easily compared.

Digital techniques may be less important for pharmacological stress echocardiography. A video recording allows good quality studies. With pharmacological stress, image quality is less affected by artifacts due to chest movements, hyperventilation or tachycardia.

METHODS USED IN THIS STUDY

In the studies reported in this thesis, stress echocardiography (either with exercise or with pharmacological agents) and myocardial perfusion scintigraphy have been performed in different groups of patients and in different clinical conditions. Some practical aspects on the protocols of echocardiographic tests are briefly reported.

Exercise protocol

Baseline blood pressure, 12-lead ECG, and cross-sectional echocardiogram are recorded at rest, with the patient lying on the left lateral decubitus. Position of precordial ECG leads is adapted in order to avoid interference with acoustic windows. All standard views are obtained (parasternal long- and short-axis, apical four- and two-chamber), when possible, and recorded on videotape and digitized on-line. Then, symptom-limited upright bicycle exercise testing is performed. Approximately one minute before the test is stopped, radiotracer (either 201-Tl or 99m-Tc-MIBI) is injected in an antecubital vein while the patient continues to exercise. Immediately after the end of the test, the patient layes in the same left lateral position on the bed, and stress images are acquired. For simultaneous nuclear studies, acquisition is done after 5 minutes when 201-Tl is used, or 1 hour later, when 99m-Tc-MIBI is used.

Pharmacological protocols

Some methodological aspects are similar to both dobutamine and dipyridamole. An infusion line is placed in an antecubital vein and the ECG is monitored throughout the test. Twelve-lead ECG is recorded with the same modalities as for exercise testing. Blood pressure is recorded from the arm not receiving the drug. Baseline echocardiogram is recorded on videotape. Digital acquisition is obtained, when needed.

Some end-points of the test are common to both drugs: chest pain, typical ST segment changes, significant side effects, completion of the protocol, and obvious stress-induced wall motion abnormalities. Antidotes (amynophylline for dipyridamole, betablockers for dobutamine) and nitrates are at hand, and all the equipment for cardiopulmonary resuscitation should be readily available.

Dobutamine stress test

Dobutamine is injected by an infusion pump with stepwise increments. The protocol used at the Thoraxcenter has changed throughout these studies. In the first patients we started with an initial infusion rate of 5 mcg/Kg/min. Every 3 minutes the infusion rate was increased with increments of 5 mcg/Kg/min, until an infusion rate of 40 mcg/Kg/min was reached. A negative test could therefore last up to 24 minutes. In a later group of patients the protocol was shortened by starting the first infusion step at 10 mcg/Kg/min and using increments of 10 mcg/Kg/min. Hence, the protocol was shortened to 12 minutes. In case the target heart rate was not reached, and the test was still negative, duration of the highest infusion rate was prolonged up to 6 minutes, while atropine (0.25-1 mg iv) was added to obtain a more pronounced chronotropic effect.

Metoprolol is injected to reverse long-lasting myocardial ischaemia and severe side effects.

Dipyridamole stress test

Patients referred for a dipyridamole test had to stop theophylline drugs at least 48 hours before the test and were not allowed to take any caffeine-containing beverages at least 12 hours prior to the test. In our laboratory, dipyridamole was injected at an infusion rate of 0.14 mg/Kg/min for 6 minutes (total dose 0.84 mg/Kg). This is not the standard protocol for the dipyridamole stress echocardiography, and it was used in patients primarily referred for myocardial scintigraphy. Aminophylline was injected in case of prolonged ischaemia (240 mg) or severe side effects, and also in the negative tests (70 mg) at the 15th minute, to abolish completely the haemodynamic effects of the dipyridamole.

STUDIES PRESENTED IN THIS THESIS

This thesis presents the initial experience on stress echocardiography done at the Department of Cardiology, University Hospital of Rotterdam. The main purposes of this research were:

1) to assess the safety and feasibility of stress echocardiography;
2) to evaluate the sensitivity and specificity of stress echocardiography for the detection of coronary artery disease;
3) to compare the results of stress echocardiography with those obtained at myocardial perfusion scintigraphy;
4) to compare the results of different pharmacological stress agents in the same group of patients.

PATIENT STUDY GROUPS IN THE PRESENT THESIS

STRESS MODALITY	STUDY	PATIENTS SELECTION	Nr OF PTS
Exercise	Ch 2	Referred for scintigraphy (suspected ischaemia) *non-diagnostic X-test *equivocal X-test *positive X-test	103
Exercise	Ch 3	Referred for scintigraphy *normal ECG at rest *coronary angiography	75
Exercise	Ch 4	One-vessel disease	44
Exercise	Ch 5	Isolated LAD stenosis (derived from Ch 4)	21
Exercise	Ch 6	Candidates for PTCA Pre- and post-PTCA	26
Dobutamine	Ch 8	Chest pain Referred for angiography	52
Dobutamine/Dipyridamole	Ch 9	Chest pain Referred for angiography	46
Dobutamine	Ch 10	Referred for scintigraphy Suspected ischaemia	105
Dipyridamole	Ch 11	Risk stratification Early post-MI	89

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PART TWO

EXERCISE ECHOCARDIOGRAPHY

CHAPTER 2

The comparative value of exercise echocardiography and 99m Tc MIBI single photon emission computed tomography in the diagnosis and localization of myocardial ischaemia.

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The comparative value of exercise echocardiography and 99m Tc MIBI single photon emission computed tomography in the diagnosis and localization of myocardial ischaemia

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KEY WORDS: Exercise echocardiography, Tc 99 m-MIBI, SPECT, myocardial ischaemia.

To determine the relative value of exercise two-dimensional echocardiography and 99m Tc methoxyisobutylisonitrile single photon emission computed tomography (MIBI SPECT) for the detection of myocardial ischaemia, 103 consecutive patients with either proven or suspected coronary artery disease, who were referred for perfusion scintigraphy, were studied by a combination of the two techniques during the same symptom-limited upright bicycle exercise test. Appropriate echocardiographic images were recorded both at rest and immediately post-exercise and subsequently analysed by means of digital cine loop processing. Both echocardiographic and MIBI SPECT images were visually analysed. For each technique, three different responses to exercise were defined: normal (absence of rest and exercise abnormalities); ischaemic (transient scintigraphic perfusion defects and transient wall motion abnormalities during exercise echocardiography); and fixed abnormalities (fixed scintigraphic perfusion defects; echocardiographic wall motion abnormalities at rest without worsening after exercise). To allow a valid comparison of each technique in localizing ischaemia, the left ventricle was divided into the following six major regions for both methods: anterior, posterolateral, inferior, interventricular septum (subdivided in anterior and posterior septum) and apex.

Eleven of the 103 patients had to be excluded from the final analysis because of unsatisfactory examinations: seven with non-interpretable exercise echocardiograms and four with non-interpretable MIBI SPECT images. The response to exercise was concordantly classified by both techniques in 84% of patients (k = 0·78). Exercise echocardiography revealed the presence of ischaemia in 38 and MIBI SPECT in 45 patients (agreement = 77%). When regional analysis was performed, concordance of exercise echocardiography and MIBI SPECT was observed in 91% of the 552 regions (k = 0·81), while agreement for the presence of myocardial ischaemia was lower (72%), with a trend for a higher occurrence of transient perfusion defects in posterolateral and inferior regions and in patients with previous myocardial infarction.

In the 30 patients without previous myocardial infarction who underwent coronary angiography, the sensitivities of exercise ECG, echocardiography and SPECT for the diagnosis of coronary artery disease (diameter stenosis ≥50%) were 56%, 70% and 77%, respectively.

Introduction

It has been demonstrated that reversible regional left ventricular wall motion abnormalities occur as a result of stress-induced myocardial ischaemia in both experimental and clinical studies[1–4], and that two-dimensional echocardiography can detect such wall motion abnormalities[5–11]. Thus, stress echocardiography and more particularly exercise echocardiography, the most physiological and commonly used type of stress, have been the subject of increasing interest because of the availability of computer-assisted image processing which facilitates the acquisition and analysis of two-dimensional echocardiograms[10,11]. Three previous reports have indicated that the information derived both from exercise and pharmacological stress echocardiography compares favourably with that derived from planar Tl 201 scintigraphy in the diagnosis of coronary artery disease[12–14]. However, the recent introduction of single photon emission computed tomography (SPECT) and the use of 99m Tc methoxyisobutylisonitrile (MIBI) as a myocardial perfusion agent have significantly improved the diagnostic accuracy of the scintigraphic technique for the detection of myocardial ischaemia[15,16]. So far, the agreement between exercise-induced wall motion abnormalities (detected by echocardiography) and transient perfusion defect (detected by MIBI SPECT) for the diagnosis, localization and quantification of myocardial ischaemia has not been explored.

Accordingly, the aim of this study was to establish the correlation between the two tests in a consecutive group of patients with proven or suspected coronary artery disease, who were presented for scintigraphy and in whom stress

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echocardiography and MIBI SPECT were simultaneously applied.

Methods

PATIENTS SELECTION

The study group consisted of 103 consecutive patients referred to the laboratory of nuclear cardiology at the Thoraxcenter for the evaluation of suspected myocardial ischaemia, who were simultaneously studied by exercise echocardiography and MIBI SPECT. Their ages ranged from 30 to 78 years (mean 55±9 years). There were 80 males and 23 females. Eleven patients were excluded from the analysis: seven because of inadequate echocardiographic images and four because of poor quality MIBI SPECT images. Twenty-nine patients had a previous myocardial infarction. The scintigraphic study was requested for the following clinical reasons: a previous non-diagnostic routine ECG exercise test and suspected myocardial ischaemia; the need to localize and to quantify the area of myocardial ischaemia in patients with a positive exercise test, or to assess the functional significance of coronary lesions in patients with an equivocal ECG exercise test result. At the time of the study, 52 patients were receiving antianginal therapy including beta-blockers either administered alone (12 patients) or in combination with nitrates and/or calcium channel blockers (24 patients). The other 16 patients were receiving calcium channel blockers, either alone (four patients) or in combination with oral nitrates (12 patients).

Exercise testing procedure

Symptom-limited upright bicycle ergometry was performed with stepwise increments of 20 W every minute. Twelve lead ECG and blood pressure were recorded at rest and at 1 min intervals during the exercise and recovery phases. Three ECG leads (II, V2, V5) were continuously monitored before, during and after exercise. The level of the ST segment was calculated, after signal averaging, by a computer-assisted system (Cardiovit CSG/12, Schiller). The ECG exercise test was classified as ischaemic when a ≥1 mm horizontal or downsloping ST segment depression occurred 80 ms after the J point. The test was classified as non-diagnostic in cases of atypical ST segment change or when left bundle branch block or left ventricular hypertrophy was present.

MIBI SPECT imaging at rest and after exercise

Before the exercise test, an intravenous cannula was inserted in an antecubital vein. Approximately 60 s before termination of exercise, an injection of 370 MBq of 99m Tc MIBI was administered. Ten minutes after the injection, a 5 g sorbitol tablet was given to accelerate the hepatobiliary clearance of the tracer. The exercise MIBI SPECT images were acquired, on average, 1 h after exercise. Imaging was performed with a Siemens Gammasonics single head Rota-camera (Orbiter) equipped with 37 photomultiplier tubes, a 1 cm NaI crystal and a low energy all-purpose collimator. Thirty-two projections (180° scanning) were obtained with an acquisition time of 45 s per projection. The digitizing matrix (64 x 64 word mode) was selected in the mid portion of the camera image by using a zoom factor of $\sqrt{2}$. The tomographic data were processed on a Gamma 11 computer system with a floating point processor. Transaxial tomograms were reconstructed with a commercially available SPETS package (Nuclear Diagnostics AB, Hagsten, Sweden). The direction of the left ventricle long axis was determined from two orthogonal views (anterior and lateral). Using a joy stick, the approximate centre of the left ventricle and the direction of the left ventricular long axis were determined. From these two long lines, the three-dimensional direction of the left ventricular long axis was computed. Oblique (short axis) and sagittal slices (vertical long axis), perpendicular and parallel to the long axis respectively, were reconstructed. For each patient, six oblique (short axis) slices were defined from the apex to the base and three sagittal slices from the septum to the lateral wall. For resting studies, patients were injected with 370 MBq of 99m Tc MIBI at least 24 h after the exercise study, using the same protocol.

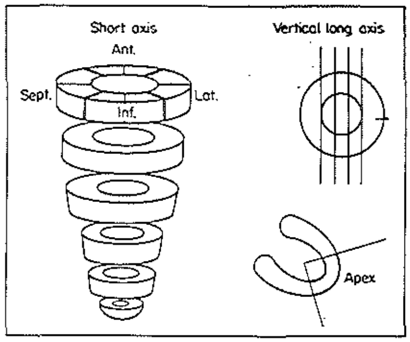

Figure 1 A diagrammatic representation of SPECT images. The six short axis slices and the three vertical long axis slices used for perfusion analysis are shown.

REST AND POST-EXERCISE ECHOCARDIOGRAPHY

Two-dimensional echocardiograms were recorded at rest and immediately after exercise, using either a 3·5 or 2·5 mHz transducer and a Hewlett Packard Sonos 1000 system. Multiple imaging planes, including conventional parasternal long and short axes, apical two- and four-chamber and apical long axis, were obtained at rest, with the patient lying in the left lateral decubitus position. Transducer positions on the chest wall, which allowed optimal imaging, were marked before the exercise test. When the transducer position coincided with the position of one of the precordial ECG leads, the ECG electrode was placed one intercostal space lower. After reaching the exercise endpoint, the patients were immediately placed in the same left lateral position and the echocardiograms

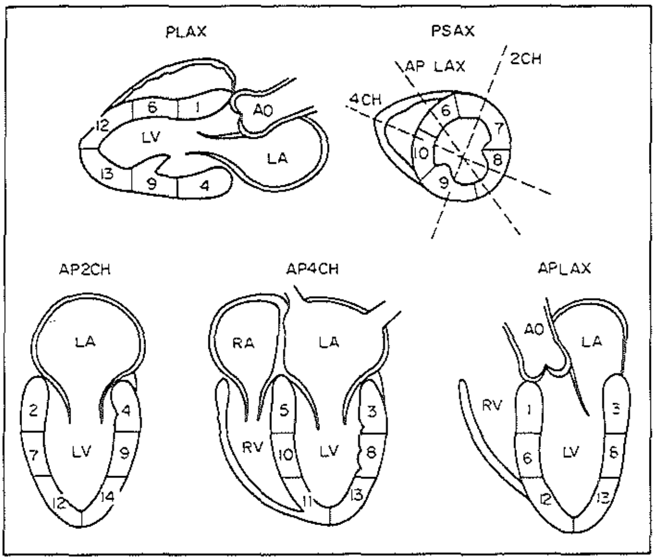

Figure 2 The 14 left ventricular segments analysed by echocardiography. The anterior region comprises segments 2 and 7; the posterolateral region, segments 3 and 8; the inferior region, segments 4 and 9; the posterior septum, segments 5 and 10; the anterior septum, segments 1 and 6; the apex, segments 11, 12, 13, 14. PLAX: parasternal long axis view; PSAX: parasternal short axis view; AP4CH: apical four chamber view; AP2CH: apical two chamber view; APLAX: apical long axis view.

were quickly repeated with the transducer in the premarked positions.

All the echocardiographic studies were recorded both on videotape and using a digital cine loop system (Nova Microsonics PreVue III, ATL). This system was set up to capture on line eight consecutive echocardiographic images with an inter-image sampling interval of 50 ms. Using this interval, the eight frames spanned a period of 350 ms after the R wave, allowing complete analysis of systole over a wide range of heart rates. Images of one representative cardiac cycle obtained from each of four different views (parasternal long axis, short axis at papillary muscle level, apical four-chamber and two-chamber) were derived at rest and served as baseline for interpretation of subsequent changes. Multiple apical views, including the apical long axis view, were used instead of parasternal views when these gave higher image quality. After exercise, the computer-based system allowed the capture of four consecutive cardiac cycles. The operator then selected the cycle with the highest image quality. Thus, two different quad screen formats showing the pre- and post-exercise views side-by-side were finally stored on a 13·4 cm, double-sided, high-density floppy disk. To analyse wall motion, these images were subsequently reviewed as a continuous loop at various play-back speeds. In addition, the videotape recordings were used to examine multiple echocardiographic views (including short axis at different levels and apical long axis views), to monitor the recovery phase and to obtain off-line digital recordings when the on line images were incomplete or technically inadequate.

INTERPRETATION OF MIBI SPECT AND EXERCISE ECHOCARDIOGRAPHY

To compare rest and exercise MIBI SPECT images, the short axis and sagittal slices were used. Each of the six short axis slices were divided into eight equal segments, yielding a total of 48 segments. The apical region was assessed from the three central sagittal cross sections, yielding a total of 48+3=51 segments (Fig. 1). One experienced observer visually assessed the uptake of radiotracer in both rest and exercise studies, giving a semi-quantitative score based on a scale of five (1=normal, 2=slightly decreased uptake, 3=moderately decreased uptake, 4=severely decreased uptake, 5='absence' of uptake). A global perfusion score index was calculated by summing the score for each segment and dividing by the number of segments analysed. A persistent perfusion defect was defined when a score ≥ 3, in one or more segments, was present both during exercise and at rest. A persisting score of 2, representing a dubious defect, was considered to be normal. Moreover, it was decided, in advance, to consider a non-reversible defect of the septal segments in the basal 2 short axis slices as normal. A perfusion defect was considered reversible when the score at rest improved by at least one grade with respect to the exercise scan. A significant but incomplete improvement of perfusion from the exercise to the rest scan (persistence of at least one segment with a score ≥ 3 in the rest scan) was regarded as an ischaemic response and, for the purpose of data analysis, included with the reversible defects.

On the echo images, the left ventricular walls were divided into 14 segments, as described by Edwards *et al.*[17] (Fig. 2). A visual analysis was performed, evaluating both systolic wall thickening and inward wall motion. Each segment was graded as normal (including hyperkinetic) = 1, hypokinetic = 2, akinetic = 3, or dyskinetic = 4. A global wall motion score index was calculated by summing the scores assigned to each segment and dividing by the number of segments visualized. The resting and post-exercise images were compared in a side-by-side manner. An ischaemic response to exercise was defined as (1) a wall motion deterioration of one or more grades in an area which was normal at rest; (2) a worsening of wall motion in a segment which was hypokinetic at rest. A normal study was defined as normal wall motion both at rest and after exercise in all ventricular regions. The patients with fixed wall motion abnormalities were classified in a third, separate group. Both tests were separately interpreted by two experienced observers, blinded to the results of any other clinical data or test results. In case of disagreement, the final interpretation was based on the judgement of a third observer.

The results obtained by the two methods were then compared. To compare the site of the perfusion abnormalities with the localization of the regional wall motion abnormalities, the 51 ventricular segments imaged by scintigraphy were combined into six major regions (Fig. 1). Similarly, the 14 echocardiographic segments were grouped into six corresponding regions, denoted as: anterior (segments 2 and 7), posterolateral (segments 3 and 8), inferior (segments 4 and 9), interventricular septum, subdivided in anterior (segments 1 and 6) and posterior (segments 5 and 10), and apex (segments 11, 12, 13, 14) (Fig. 2).

INTER- AND INTRAOBSERVER VARIABILITY OF EXERCISE MIBI SPECT AND ECHOCARDIOGRAPHY

To assess interobserver variability, 45 rest/post-exercise echocardiograms were reviewed by an independent investigator unaware of either clinical data, angiographic or MIBI SPECT results. One investigator subsequently reviewed 24 of these examinations at least 1 month after the first interpretation. Similarly, 20 MIBI SPECT examinations were assessed by two independent investigators and twice by one of them. The interobserver and intra-observer variability for the final interpretation of the tests were assessed by calculating the percentage of agreement, the κ coefficient and its standard error[18].

CORONARY ANGIOGRAPHY

Coronary angiograms using the Judkins technique were performed within 2 months in 51 patients. Significant coronary artery disease was visually defined as a diameter stenosis $\geq 50\%$.

STATISTICAL ANALYSIS

All continuous variables were expressed as mean $\pm$ SD. The agreement between MIBI SPECT and exercise echocardiography was defined as the percentage of concordant diagnoses and it was also assessed by calculating the kappa (κ) value and its standard error; κ values between 0·6 and 1 were considered indicative of good agreement. Global wall motion score indexes were compared using standard correlation statistics. McNemar's test was used to compare percentage between paired data. P values <0.05 were considered significant.

Results

FEASIBILITY AND REPRODUCIBILITY OF THE TESTS

The bicycle exercise test and echocardiographic studies were completed in all patients without complications. Seven patients were excluded from analysis because of technically inadequate post-exercise echocardiograms and four patients because of poor quality MIBI SPECT. Thus, 92 of 103 patients had analysable data with both tests and were included in this study. In 15 patients parasternal views were inadequate (in seven both at rest and after exercise and in eight only after exercise) and therefore only the apical views were analysed. The mean time intervals between the end of exercise and the recording of the first and the last echocardiographic images were 21 ± 12 and 82 ± 29 seconds respectively (ranges 8 to 42 and 32 to 140 s). During this period, heart rate decreased by 15 ± 5 beats . min^{-1}. The acquisition of stress MIBI SPECT began 1 h after peak exercise. Therefore, the immediate recovery phase could be monitored by echocardiography without interfering with the MIBI SPECT. The analysis of echocardiographic images required about 15 min for each study, and was significantly shorter than the analysis of scintigraphic studies, which required approximately 1 h including time for processing and interpretation.

Intra-observer and interobserver agreement for the final interpretation of echocardiographic images was 92% ($\kappa = 0.84$, SE $= 0.2$) and 91% ($\kappa = 0.81$, SE $= 0.14$), respectively. For MIBI SPECT, intra-observer and interobserver agreement occurred in 90% ($\kappa = 0.8$, SE $= 0.22$) and 85% ($\kappa = 0.70$, SE $= 0.23$) of patients, respectively.

RELATIONSHIPS BETWEEN WALL MOTION AND MYOCARDIAL PERFUSION

The results of exercise echocardiography and MIBI SPECT in the 92 patients are compared in Fig. 3. Overall agreement for the final diagnosis occurred in 84% of patients ($\kappa = 0.78$, SE $= 0.09$). A reversible perfusion defect was found in 45 patients (in 27 with a complete normalization of perfusion at rest); exercise echocardiography was concordantly categorized as ischaemic in 35 of them (agreement for ischaemia = 77%). Of the 10 patients with discordant results, six had a totally reversible and four a partially reversible perfusion defect. In 9 patients the site of the reversible perfusion defect was the inferior and/or the posterolateral wall. In 21 of the 35 patients who exhibited ischaemia on both tests, the site of the perfusion defect

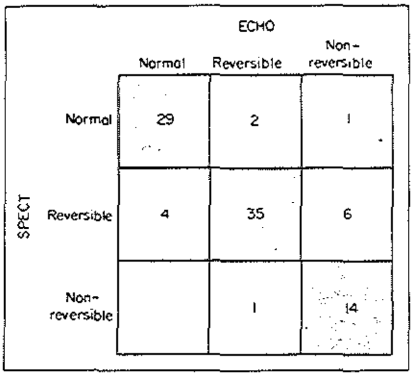

Figure 3 Comparison of the results of rest/post-exercise 99m Tc MIBI SPECT and echocardiography in 92 patients.

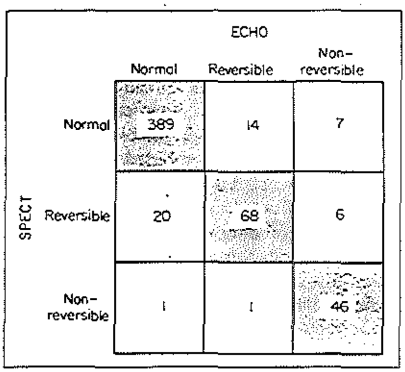

Figure 4 Comparison of rest/post-exercise perfusion and wall motion pattern in 552 left ventricular regions examined.

was identical to the site of wall motion abnormality. In 12 patients a partial concordance was found, since in at least one region both perfusion defect and wall motion abnormality were coincident. Of the remaining two patients, the first showed posterolateral wall motion abnormality with an anterior perfusion defect, the second developed apical and inferior septal wall motion abnormality while a perfusion defect was found in the posterolateral region.

Among the 552 ventricular regions analysed, the overall agreement between exercise echocardiography and SPECT was 91% and the κ value was 0·81 (SE = 0·03) (Fig. 4). Of the 94 regions with reversible perfusion defects, transient wall motion abnormalities were seen in 68 (agreement for ischaemia = 72%). The extent of the perfusion defects and of the ventricular wall motion abnormalities evaluated by means of the global score indexes correlated both at rest and after exercise ($r = 0{\cdot}86$, $P < 0{\cdot}001$; $r = 0{\cdot}79$, $P < 0{\cdot}001$).

The relation between transient wall motion abnormalities and reversible perfusion defects in the subgroups of patients with and without previous myocardial infarction are represented in Fig. 5. In both subgroups, transient perfusion defects without new or worsened wall motion abnormalities were present in five patients; the incidence tended to be higher in patients with a previous myocardial infarction (15% vs 8%, ns).

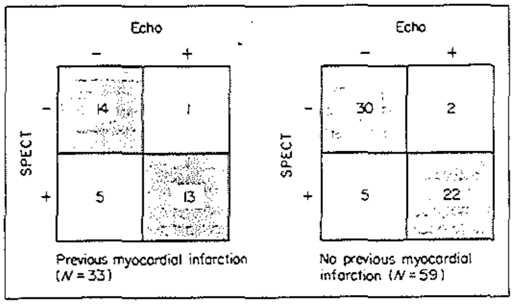

Figure 5 Agreement between transient wall motion abnormalities (Echo+) and reversible perfusion defects (SPECT+) separately analysed in patients with and without previous myocardial infarction.

RELATION OF MIBI SPECT AND EXERCISE ECHOCARDIOGRAPHY WITH ECG EXERCISE TEST

Sixty percent of the patients achieved 85% of their maximal predicted heart rate. Mean work load was 159 ± 38 W; maximal heart rate and maximal systolic blood pressure were 138 ± 25 (beats . min^{-1}) and 180 ± 28 (mmHg), respectively. According to the symptoms and ECG changes induced by the exercise test, 39 patients had ischaemia, 27 had a non-diagnostic result, and 26 were normal. Figure 6 shows the relation of exercise ECG test to MIBI SPECT and echocardiographic results.

CORONARY ANGIOGRAPHIC FINDINGS

Of the 55 patients who underwent coronary angiography, significant coronary artery disease was present in 51. Among 30 patients without previous myocardial infarction, the sensitivities of ECG changes, echocardiographic changes and transient perfusion defects on SPECT imaging for the detection of coronary artery disease were 56%, 70% and 77%, respectively.

Discussion

Myocardial perfusion scintigraphy is used to improve the accuracy of exercise testing to diagnose ischaemia due to coronary artery disease. The widespread usage of perfusion scintigraphy is limited by the high cost of the procedure, the exposure of the patients to radiation, and the need for nuclear medicine facilities which are not available in all centres. Echocardiography, performed in conjunction with different kinds of stress, has been proposed as a feasible, safe and low cost alternative technique. This prospective study was undertaken to compare exercise echocardiography, integrated with a cine loop acquisition system, to MIBI SPECT in terms of their ability to elicit

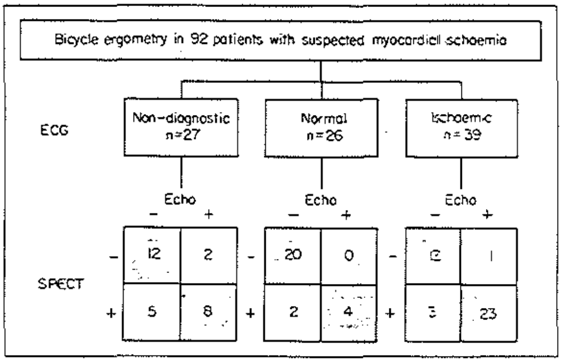

Figure 6 Comparison of rest/post-exercise SPECT and echocardiography in patients with different ergometric responses.

an ischaemic response. Our data demonstrate that exercise echocardiography and MIBI SPECT provide similar information about the response to exercise and confirm the few studies so far reported which compare stress echocardiography with perfusion scintigraphy[12–14]. However, the methodology and part of the results of the present investigation differ from previous studies in several aspects.

Our primary goal was to establish the potential role of exercise echocardiography as an alternative to perfusion scintigraphy. Thus, our study group included patients referred for radionuclide study rather than coronary angiography. Therefore, we did not use coronary angiography as a standard. Instead, we compared the functional consequences of myocardial ischaemia detected by the two non-invasive methods. Since a new wall motion abnormality detected by exercise echocardiography represents a functional consequence of myocardial ischaemia, it seems more appropriate to relate exercise echocardiography to perfusion studies than to the coronary anatomy alone.

Secondly, we used SPECT imaging with 99m Tc MIBI as perfusion tracer, whereas prior correlative studies employed Tl 201 planar scintigraphy. This tomographic method avoids the superimposition of individual ventricular walls and provides better definition of specific regions, thus providing more sensitivity for the detection of individual coronary artery stenoses[15,16]. Moreover, when 99m Tc MIBI is used instead of Tl 201 as a myocardial perfusion tracer, myocardial definition is improved and ischaemic segments are better differentiated from fixed perfusion defects[16].

Thirdly, echocardiographic images were obtained and myocardial perfusion defined with 99m Tc MIBI SPECT during the same exercise test. Also, echocardiograms were recorded and displayed using a digital cine loop system, thus reducing the interference of post-exercise tachypnoea and allowing side-by-side comparison of rest and post-exercise images. This improves the quality of the exercise echocardiography and facilitates the analysis.

In the present study, satisfactory echocardiograms were obtained in 93% of patients; this is consistent with the success rate reported by other investigators using comparable methodology[6]. It is worth noting that in the present study no patient was excluded from analysis on the basis of poor image quality on the resting echocardiogram. Also, the results of post-exercise echocardiography are strongly dependent on the ability of the operator to record good quality images quickly after exercise is stopped. Despite these limitations, echocardiography is feasible immediately after upright bicycle ergometry in most patients and can be combined with simultaneous MIBI SPECT. It has been documented that delayed image acquisition can reduce the sensitivity of Tl 201 scanning to detect perfusion abnormalities[19] whereas 99m Tc MIBI allows imaging 1 h after the injection. Therefore, MIBI SPECT is more suitable than Tl 201 for correlative echocardiographic studies.

RELATIONSHIP OF MYOCARDIAL PERFUSION TO REGIONAL LEFT VENTRICULAR FUNCTION

The results of the present study indicate a good correlation between regional perfusion and regional wall motion, both at rest and after exercise, consistent with previous findings with stress/redistribution planar Thallium scintigraphy[12] and with Thallium SPECT imaging at rest[20]. In addition, the data of the present study suggest that MIBI SPECT detects more patients, and more ventricular regions, with 'ischaemia'. This is especially true in patients with previous myocardial infarction or when 'ischaemia' occurs in the inferior or posterolateral regions.

There are several explanations for 'false-negative' echocardiographic studies, such as the rapid recovery of small exercise-induced wall motion abnormalities[9,21] and hyperdynamic contraction of normally perfused segments adjacent to the site of new wall motion abnormalities. Moreover, in patients with previous myocardial infarction, exercise-induced wall motion abnormalities are difficult to detect because of significant wall motion abnormalities at rest.

Finally, it should be underlined that perfusion imaging detects maldistribution of flow, which is not always accompanied by new wall motion abnormalities, which are the mechanical consequence of a real ischaemia.

STUDY LIMITATIONS

Some limitations of the present study should be acknowledged. First of all, both regional wall motion and myocardial perfusion were assessed visually. A more objective method would be desirable, but is not yet available. Quantitative analysis of exercise wall motion assessed by echocardiography has been attempted in normal individuals[22]. However, the qualitative approach has been preferred by the majority of the investigators[6–10]. The difficulty of correcting for cardiac motion, which is accentuated by fast breathing, hampers the application of algorithms for quantitative regional wall motion analysis. Conversely, our experience and that of other laboratories indicates that quantitative MIBI SPECT produces reliable information[23].

Secondly, coronary angiography was not used as the 'gold standard' in all patients. However, we do not feel this is a major limitation, since our goal was to compare the value of two different tests to assess the functional significance of coronary disease. It would not be correct to assess the diagnostic value of the tests in patients in which the application of coronary angiography was strongly dependent on the test results. Moreover, we have previously assessed the diagnostic accuracy of the two methods[24].

In conclusion, this study indicates generally good agreement between echocardiography and MIBI SPECT with respects to the response to exercise. Agreement is highest when the tests are normal or show fixed abnormalities. However, SPECT imaging may detect 'ischaemia' more frequently than echocardiography, particularly in inferior and posterolateral regions and in the presence of previous myocardial infarction.

We are most grateful to Margriet Straver and Marion Verdijsseldonck for their friendly support and technical assistance during this study.

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CHAPTER 3.

Exercise echocardiography and technetium-99m MIBI single-photon emission computed tomography in the detection of coronary artery disease.

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Am J Cardiol 1991;67:350-5.

Exercise Echocardiography and Technetium-99m MIBI Single-Photon Emission Computed Tomography in the Detection of Coronary Artery Disease

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To compare the relative diagnostic value of exercise echocardiography with perfusion technetium-99m metoxyisobutylisonitrile single-photon emission computed tomography (SPECT) in detecting coronary artery disease (CAD), 75 patients with suspected CAD but a normal electrocardiogram (ECG) at rest were included in a prospective correlative study. Both the exercise echocardiograms and SPECT studies were performed in conjunction with the same symptom-limited bicycle exercise test. The development of either a new wall motion abnormality or a reversible perfusion defect after exercise, or both, were regarded as a positive test for the exercise echocardiographic and SPECT studies, respectively. The results of these 2 diagnostic tests were compared with coronary arteriography.

Exercise echocardiography identified 35 (71%) and SPECT 41 (84%, p = 0.13) of the 49 patients with significant CAD (defined as >50% diameter stenosis). Twenty-five of the 26 patients (96%) without significant coronary stenosis had negative exercise echocardiographic results and 23 of 26 (88%) had negative SPECT results. Exercise-induced new wall motion abnormalities showed a good correlation with reversible perfusion defects, and the results of the 2 methods were concordant in 65 of 75 patients (agreement = 88%, $\kappa = 0.75 \pm 0.14$). Both the diagnostic accuracy of exercise echocardiography and SPECT were significantly higher than the exercise ECG (81 vs 64%, p < 0.02 and 88 vs 64%, p < 0.005). The sensitivity and specificity for detecting individual diseased vessels were 60 and 95% for exercise echocardiography and 67 and 94% for SPECT. However, in the 33 patients with 1-vessel disease, exercise echocardiography showed a lower sensitivity when compared with SPECT (61 vs 82%, p <0.02). SPECT was tendentially more sensitive than exercise echocardiography in detecting isolated left circumflex coronary artery stenoses.

(Am J Cardiol 1991;67:350–355)

Myocardial perfusion scintigraphy and, more recently, exercise echocardiography have been widely applied in the noninvasive diagnosis of coronary artery disease (CAD). Important technologic developments have occurred in both techniques that have improved the quality of the images and thus enhanced their diagnostic value. Single-photon emission computed tomography (SPECT), by eliminating the superimposition of different myocardial regions inherent in planar scintigraphy, has improved the nuclear technique to diagnose and localize significant CAD.[1–3] The improvement of the echocardiographic equipment and the development of digital cine loop acquisition systems have overcome some of the practical and technical problems that had previously limited the application of exercise echocardiography.[4–6] Thus far, only limited data concerning the direct comparison of exercise echocardiography and planar 201-thallium scintigraphy are available.[7,8] However, the relative value of exercise echocardiography with a digital cine loop system versus SPECT imaging for the definition of CAD (for clinical decision making) has not been determined. We performed exercise echocardiography and SPECT during the same exercise test in a group of patients with clinically suspected CAD and a normal electrocardiogram (ECG) at rest. Their relative values in identifying and localizing significant coronary artery stenoses was the aim of this study.

METHODS

Study group: Between August 1989 and January 1990, 169 patients primarily referred for stress perfusion scintigraphy underwent simultaneous exercise echocardiography and SPECT imaging in our laboratory. Of the 93 patients in whom coronary angiography was performed within 2 months of the noninvasive studies, the 75 who had a normal ECG at rest (including flat T waves) were selected for the current study.

The mean age ± standard deviation of the 75 patients (65 men and 10 women) was 52 ± 12 years.

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Fourteen had a documented previous non-Q-wave myocardial infarction. At the time of the study, 27 patients were receiving antianginal therapy, including β blockers administered either alone (8 patients) or in combination with nitrates or calcium antagonists (9 patients). The remaining 9 patients were receiving calcium antagonists either alone (4 patients) or in combination with oral nitrates (5 patients). One patient was taking digitalis.

Exercise test procedure: All patients underwent a symptom-limited upright bicycle ergometry test with stepwise increments of 20 W each minute. Three electrocardiographic leads (lead II, V_2 and V_5) were continuously monitored. The level of the ST segment was calculated averaging the signal by a computerized system (Cardiovit CSG/12, Schiller). An ischemic response was defined as a ≥1 mm horizontal or downsloping ST depression persisting 80 ms after the J point.

SPECT imaging: Approximately 1 minute before the termination of the exercise, 370 mBq of technetium-99m metoxyisobutylisonitrile (MIBI) was injected into an antecubital vein. The exercise MIBI SPECT images were acquired 1 hour after exercise. Imaging was performed with a Siemens Gammasonics single-head Rota-Camera (Orbiter) equipped with 37 photomultiplier tubes, ⅜-inch NaI crystal and a low energy all-purpose collimator. Thirty-two projections with 6° increments (180° scanning) were obtained with acquisition time of 45 seconds per projection. The digitizing matrix (64 × 64 word mode) was selected in the midportion of the camera image by using a zoom factor $\sqrt{2}$. The tomographic data were processed on a Gamma 11 computer system with a floating point processor. Transaxial tomograms were reconstructed with the commercially available SPETS package (Nuclear Diagnostics AB, Hagsten, Sweden). The direction of the left ventricular long axis was determined from 2 orthogonal views (anterior and lateral). Oblique slices (short axis) and sagittal slices (vertical long axis), perpendicular and parallel to the long axis, respectively, were reconstructed. For each patient studied, 6 oblique (short axis) slices were defined from the apex to the base and 3 sagittal slices from the septum to the lateral wall.

For resting studies, patients were injected at rest with 370 mBq MIBI ≥24 hours apart from the exercise studies.

Exercise echocardiography: Two-dimensional echocardiograms were obtained at rest and immediately after the exercise test with the patients lying in the left lateral decubitus position. Multiple imaging sections, including conventional parasternal long and short axes, apical 2- and 4-chamber and apical long-axis planes were used. All images were obtained with a commercially available echocardiographic system (Hewlett Packard Sonos 1000). The rest and exercise images were both recorded on videotape and digitized on-line with a Nova Microsonics PreVue III System (ATL Co.). This system allows the recording at rest of 1 representative cardiac cycle obtained from 4 different views. After peak exercise, the digital system allowed the capture of 4 consecutive cardiac cycles for each view. The cycle with the best image quality could then be selected and displayed side by side with the correspondent rest images. Two different quad screen formats, showing the images before and after exercise, were finally stored in a 5¼-inch double-sided high-density floppy disk and subsequently reviewed as a continuous loop at various playback speeds.

Coronary angiography: All coronary angiograms were recorded using the Judkins technique. Significant CAD was visually defined as ≥50% narrowing of the luminal diameter of ≥1 coronary arteries or of 1 of their major branches.

Interpretation of exercise echocardiography and SPECT: The analysis of the echocardiographic images was performed by 1 experienced observer unaware of scintigraphic and angiographic data. Left ventricular wall motion was visually evaluated and graded as normal = 1, hypokinetic = 2, akinetic = 3, and dyskinetic = 4. A postexercise wall motion score index was calculated by summing the scores assigned to each segment and dividing by the number of segments. By comparing in a side-by-side manner the rest and postexercise images, an ischemic response was defined as the development of a new wall motion abnormality in the study after exercise.

To compare rest and exercise SPECT images, the short- and the vertical long-axis slices were used. Each of the 6 short-axis slices were divided into 8 equal segments, yielding a total of 48 segments. The apical region was assessed from the 3 central sagittal cross sections, yielding a total of 51 segments. All the SPECT studies were interpreted by 2 experienced observers, unaware of echocardiographic and angiographic results, using a 5-point visual scoring system (1 = normal, 2 = doubtfully decreased uptake, 3 = mildly decreased uptake, 4 = severely decreased uptake, and 5 = "absence" of uptake). A semiquantitative score index was calculated by summing the score of each segment and dividing by the number of all the segments. An ischemic response was diagnosed when the stress images showed a significant perfusion defect (score ≥3 in ≥2 contiguous segments), which partially or completely normalized in the rest images.

In our laboratory inter- and intraobserver agreement for exercise echocardiography was 91% (κ = 0.81, standard error of the mean [SEM] = 0.14) and 92% (κ = 0.84, SEM = 0.2) for exercise echocardiography and 85% (κ = 0.70, SEM = 0.23) and 90% (κ = 0.8, SEM = 0.22) for SPECT.

Assignment of different left ventricular region to specific coronary arteries: To assign the vascular territories of the different coronary arteries, the 51 left ventricular segments, imaged by SPECT, were combined in 5 major regions (Figure 1). Similarly, the 14 echocardiographic segments were grouped in the same corresponding ventricular regions, denoted as: anterior (segments 2 and 7), posterolateral (segments 3 and 8), inferior (segments 4 and 9), interventricular septum, which was subdivided into anterior (segments 1 and 6) and posterior (segments 5 and 10), and apex (segments 11, 12, 13 and 14) (Figure 2).

For both techniques, the vascular territory of the left anterior descending artery included the anterior wall and anterior septum; the inferior wall was considered to

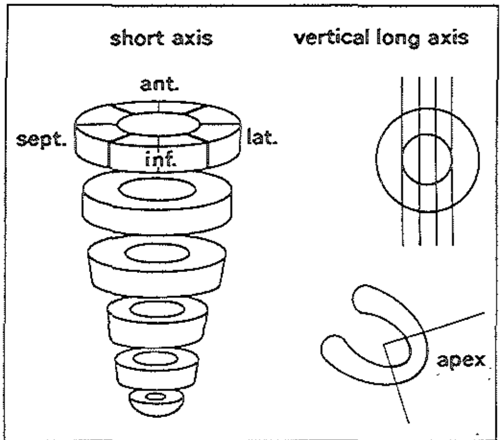

FIGURE 1. Representation of single-photon emission computed tomography imaging. The 6 short-axis and the 3 vertical long-axis slices were used for analysis of the studies. The left ventricle was divided into 5 major regions: interventricular septum (sept.), anterior (ant.) wall, lateral (lat.) wall, inferior (inf.) wall and apex.

TABLE I Overall Diagnostic Values for Coronary Artery Disease of Digital Exercise Echocardiography, SPECT and Electrocardiogram

	Sensitivity	Specificity	Accuracy
ECHO	71% (35/49)	96% (25/26)	81% (61/75)
SPECT	* 84% (41/49)	88% (23/26)	88% (65/75) †
	‡		‡
ECG	55% (27/49)	81% (21/26)	64% (48/75)

* = p <0.05; † = p <0.02; ‡ = p <0.005.
ECG = electrocardiogram; SPECT = single-photon emission computed tomography.

represent the vascular bed of the right coronary artery and the posterolateral wall of the left circumflex artery. The attribution of the posterior septum and of the apex was more flexible, depending on the coexistent abnormalities in the adjacent regions. In case of an isolated apical defect, the defect was attributed to the vascular territory of the left anterior descending artery.

Statistical analysis: McNemar's test was used to assess the significance of the differences between sensitivities, specificities and accuracies. P values <0.05 were considered significant. The agreement between techniques was defined as the percentage of concordant diagnosis and it was also assessed by calculating the κ value and its SEM. Wall motion and perfusion score indexes were compared using standard correlation statistics.

RESULTS

No adverse clinical consequences resulted from the exercise testing. Thirty-four patients (45%) attained at least the 85% of their age-predicted maximal heart rate. Angina pectoris occurred in 16 (21%) and ischemic ST-segment depression in 32 patients (43%). The intervals between the end of the exercise and the recording of the first and the last echocardiographic images were 22 ± 13 seconds (range 6 to 50) and 80 ± 33 seconds (range 35 to 150), respectively. The rest echocardiograms showed normal left ventricular wall motion in 71 patients; 4 patients had mild localized wall motion abnormalities (hypokinesia of 1 or 2 segments), whereas definite perfusion defects in the rest scan were found in 5 patients. In all these patients a worsening of wall motion and perfusion was seen after exercise. Resting wall motion and perfusion abnormalities were concordant with

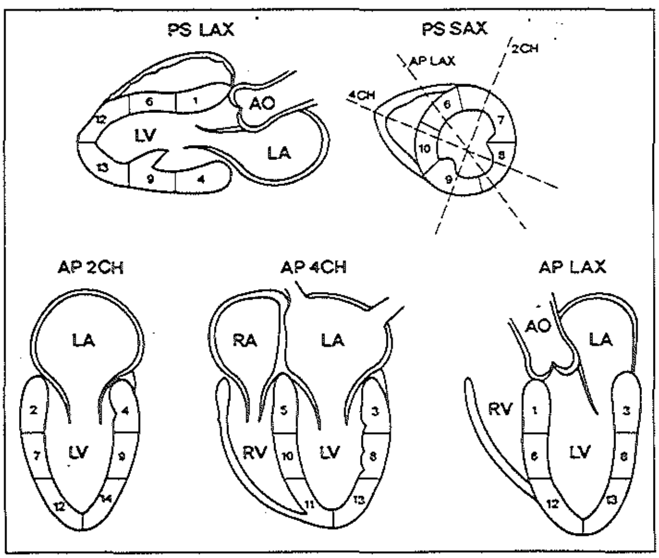

FIGURE 2. The 14 left ventricular segments analyzed by echocardiography. Anterior region comprised segments 2 and 7; posterolateral, segments 3 and 8; inferior region, segments 4 and 9; posterior septum, segments 5 and 10; anterior septum, segments 1 and 6; apex, segments 11, 12, 13 and 14. AO = aorta; AP4CH = apical 4-chamber view; AP2CH = apical 2-chamber view; APLAX = apical long-axis view; LA = left atrium; LV = left ventricle; PSLAX = parasternal long-axis view; PSSAX = parasternal short-axis view; RA = right atrium; RV = right ventricle.

TABLE II Ergometric, Scintigraphic and Angiographic Data in Patients with False-Negative Exercise Echocardiography

Pt. No.	MW (W)	%MHR (beats/min)	AP	ST	BB	SPECT	LAD	LC	Right	Time from Exer. to Echo*
1	160	59	+	0	0	0	+	+	0	20–60
2	140	99	0	0	0	0	0	0	+	13–58
3	160	90	0	+	0	+(PL)	0	+	0	24–114
4	150	80	0	0	0	+(PL)	0	0	+	32–110
5	160	90	0	0	0	0	0	+	0	16–83
6	120	100	0	0	0	0	0	+	0	12–50
7	180	70	0	+	0	0	0	+	0	10–50
8	140	80	+	0	0	0	+(diag)	0	0	30–110
9	140	81	0	+	+	+(S,A)	+	0	0	20–120
10	160	91	0	+	0	+(I)	0	+	0	15–60
11	140	82	0	+	0	0	+	0	0	30–120
12	140	90	0	0	+	+(PL)	0	+	0	30–85
13	100	64	0	0	+	+(PL)	0	+	0	20–115
14	148	60	0	+	+	+(PL,A)	0	+	0	15–115

* The numbers represent the time interval (seconds) between the peak exercise and the acquirement of the first and of the last echocardiographic view, respectively.
A = anterior; AP = angina pectoris; BB = β blockers; Diag = diagonal branch; exer. = exercise; I = inferior; LAD = left anterior descending artery; LC = left circumflex artery; MHR = maximal heart rate; MW = maximal work load; OM = obtuse marginal branch; PL = posterolateral; Right = right coronary artery; S = septal; SPECT = single-photon emission computed tomography; ST = ST segment.
+/0 = presence/absence of angina, ST-segment depression, β-blocker therapy, transient perfusion defect, coronary diameter stenosis >50%.

the site of infarction in 3 and 4 patients, respectively. Forty-nine patients (65%) had >50% diameter stenosis of ≥1 of the coronary arteries; of these, 16 had a multiple vessel disease. Twenty-six had either normal or not significantly diseased vessels.

Sensitivity and specificity for the identification of coronary artery disease: The overall sensitivity, specificity and accuracy of exercise echocardiography, SPECT and electrocardiography in detecting CAD are listed in Table I. Exercise echocardiography and SPECT showed sensitivities of 71 and 84% ($p = 0.13$), which were significantly higher than that obtained by ECG ergometry (55%, $p < 0.05$ and $p < 0.005$, respectively). Among the 26 patients without significant CAD, 25 had normal exercise echocardiography and 23 normal SPECT. The overall accuracies of 81% for echocardiography and of 88% for SPECT were significantly greater than by exercise ECG.

The effect of the number of abnormal vessels present on the ability to obtain an ischemic response by the different techniques is shown in Figure 3: In patients with 1-vessel disease, SPECT showed a greater sensitivity than exercise echocardiography ($p < 0.05$). In patients with multiple vessel disease, 15 and 14 of 16 were identified, respectively, as ischemic by exercise echocardiography and SPECT. Table II summarizes the ergometric, scintigraphic and angiographic data in the 14 patients with false-negative echocardiographic results. Nine of these had negative ECGs and 7 also had false-negative SPECT. A 1-vessel disease was found in 13 patients and only 1 patient had multivessel disease.

Agreement between echocardiography and SPECT for the diagnosis of ischemia: Figure 4 shows the relation between the final diagnosis provided by exercise echocardiography and SPECT. Sixty-five of 75 patients were concordantly classified (agreement = 88%, $\kappa \pm$ SEM $= 0.75 \pm 0.14$). In the 35 patients with ischemic response detected by the 2 methods, wall-by-wall com-

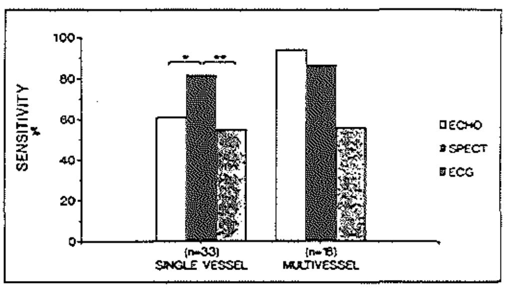

FIGURE 3. Comparison of the sensitivities of exercise echocardiography (ECHO), single-photon emission computed tomography (SPECT) and electrocardiography (ECG) in patients with 1- and multivessel disease. * = p <0.05; ** = p = 0.02.

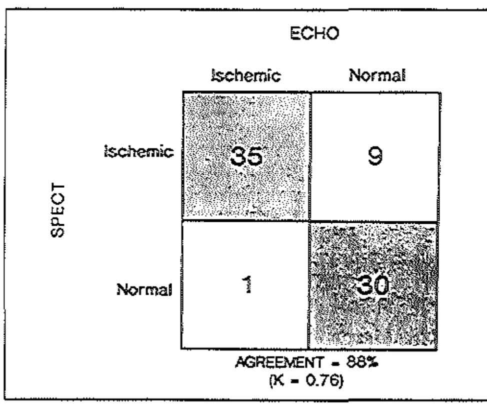

FIGURE 4. Agreement between exercise echocardiography (ECHO) and single-photon emission computed tomography (SPECT) in diagnosing ischemia.

TABLE III Detection of Individual Coronary Artery Stenoses with Exercise Echocardiography and SPECT						
	Echocardiography			SPECT		
	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
Total	60 (42/70)	95 (146/155)	84 (188/225)	64 (47/70)	94 (145/155)	85 (192/225)
LAD	69 (20/29)	98 (45/46)	87 (65/75)	66 (19/29)	96 (44/46)	84 (63/75)
LC	45 (11/24)	96 (49/51)	80 (60/75)	67 (16/24)	96 (49/51)	87 (65/75)
Right	65 (11/17)	89 (52/58)	84 (63/75)	70 (12/17)	89 (52/58)	85 (64/75)

Values are expressed as percentage and as absolute numbers.
Abbreviations as in Table II.

parison of transient wall motion and perfusion defects demonstrated a complete correspondence in 28, a partial correspondence in 5 and no correlation in 2. When the exercise wall motion and perfusion scores indexes were compared, they were positively correlated ($r = 0.75$; $p < 0.001$).

Localization of individual coronary artery stenoses: The detection of individual narrowed arteries by each technique is presented in Table III. Exercise echocardiography correctly identified 42 of the 70 stenosed arteries (60%) and 146 of the 155 normal vessels (95%). SPECT correctly identified 47 of the 70 stenosed arteries (67%) and 145 of the 155 normal vessels (94%).

Figure 5 shows the comparison of the sensitivities for individual lesions in patients with 1-vessel disease. In this subset, only 5 of 13 left circumflex lesions were detected by exercise echocardiography, whereas SPECT correctly identified 10 of them ($p = 0.07$). In contrast, both techniques showed a similar ability to predict left anterior descending and right coronary artery stenoses.

DISCUSSION

This is the first study in which exercise echocardiography and technetium-99m SPECT imaging have been simultaneously tested to detect the presence of CAD in a large group of patients with a normal ECG at rest. The main findings of this study are (1) that stress echocardiography and SPECT have a good agreement and have a similar diagnostic accuracy, which is superior to that of exercise electrocardiography (Table I), and (2) that SPECT is only slightly superior to exercise echocardiography in detecting 1-vessel disease in patients with a stenosis of the left circumflex coronary artery (Figure 5).

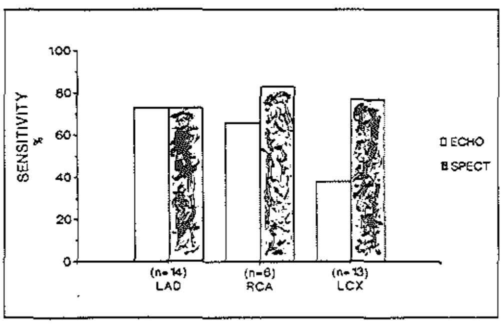

FIGURE 5. Detection of individual coronary artery stenosis by exercise echocardiography (ECHO) and single-photon emission computed tomography (SPECT) in patients with 1-vessel disease. LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

In a study by Maurer and Nanda,[7] exercise echocardiography and planar thallium-201 scintigraphy were performed in a group of patients referred for coronary arteriography. The tests provided a sensitivity of 83 and 78%, respectively. They found a sensitivity for exercise echocardiography that was better than in our study (83 vs 71%), whereas our SPECT results had a similar sensitivity when compared with planar scintigraphy used in their study (84 vs 78%). However, the results of these studies are difficult to compare directly because of different patient selection: our patients were primarily referred for stress scintigraphy, whereas patients in the other study were primarily referred for coronary arteriography, and more severe CAD may have been present. This can account for the slightly better results of exercise echocardiography relative to perfusion imaging in the study by Maurer and Nanda. Similar results have been reported by other investigators.[4,5,9] Recently, Ryan et al,[6] in patients with chest pain and normal left ventricular wall motion at rest, found a sensitivity of 78% and a specificity of 100% compared with lesions of >50% on coronary arteriography. In addition, these investigators found the lowest sensitivity in patients with 1-vessel disease of the left circumflex coronary artery, which is consistent with our findings. Furthermore, the use of antiischemic drugs may reduce the sensitivity of both perfusion scintigraphy and stress echocardiography.[10,11]

We found that SPECT has higher sensitivity than echocardiography in detecting patients with 1-vessel disease. Transient perfusion defects may occur early and do not always lead to a wall motion abnormality. The latter results when more pronounced ischemia is present. Thus, exercise echocardiography may be negative when a perfusion defect is detected, which may explain its lower sensitivity. In some patients, wall motion abnormalities recover very rapidly after the cessation of exercise, which may further explain a lower sensitivity of stress echocardiography, because its acquisition is done in the immediate postexercise phase and not at peak exercise.[12]

In contrast to patients with 1-vessel disease, echocardiography and SPECT had a similar diagnostic efficacy in patients with multiple vessel disease. Moreover, in this study few patients with multiple vessel disease were included and therefore the results cannot be considered conclusive.

Study limitations: Our patients were referred for scintigraphy for a variety of reasons, such as a nondiagnostic electrocardiographic exercise test, the localization and quantification of ischemia, and the assessment of the functional significance of the coronary stenosis before intervention. Thus, the results cannot be directly compared with patients selected on the basis of other criteria. Second, both exercise echocardiography and SPECT studies were visually analyzed. Although the quantitative analysis of exercise echocardiograms is hampered by technical difficulties, its application to SPECT has enhanced its diagnostic power.[2]

In conclusion, exercise echocardiography and SPECT, directly compared in a series of patients with a normal ECG at rest, provide similar overall information for the noninvasive diagnosis of CAD. A strong correlation between the 2 techniques for identifying localizing and quantifying ischemia was found. SPECT imaging, however, appears to be superior to exercise echocardiography in patients with 1-vessel disease, particularly of the left circumflex coronary artery.

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CHAPTER 4.

Relationship between exercise echocardiography and perfusion single-photon emission computed tomography in patients with single-vessel coronary artery disease.

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Am Heart J 1992;124:75-83.

Relationship between exercise echocardiography and perfusion single-photon emission computed tomography in patients with single-vessel coronary artery disease

The aim of this study was to assess the relative value of exercise echocardiography and perfusion single-photon emission computed tomography (SPECT) in identifying the presence and severity of coronary artery stenosis. Accordingly, 44 consecutive patients with stenosis in one vessel performed simultaneous postexercise echocardiography and perfusion SPECT (with either thallium-201 [$n = 19$] or 99m-Tc-methoxyisobutyl isonitrile [$n = 25$]) in conjunction with symptom-limited bicycle exercise testing. Positive test results were based on the presence of new or worsened exercise-induced wall motion abnormalities and transient perfusion defects, respectively. Moreover, an "ischemic" score index was derived for semiquantitative assessment of both echocardiography (with a 14-segment model of left ventricular wall on a 4-point scale) and SPECT (47-segment model on a 5-point scale). All patients underwent correlative coronary arteriography, assessed by digital caliper. Significant coronary artery disease (diameter stenosis ≥50%) was present in 30 patients. There was a good overall concordance between the two tests in terms of result (79%); compared with patients with positive results of both tests, in the seven patients with positive SPECT and negative echocardiography the time of recording echocardiographic images was longer ($p = 0.05$). When analyzing patients according to the percent diameter stenosis (>70%, 50% to 70%, and <50%) for both echocardiography and SPECT, the prevalence of an ischemic response was directly related to the severity of the coronary stenosis ($p < 0.001$); moreover, a negative test result was highly predictive of a diameter coronary stenosis less than 70%. A fair correlation was found between percent diameter stenosis and both ischemic wall motion and perfusion score indexes ($r = 0.62$, $p < 0.001$; $r = 0.51$, $p < 0.001$, respectively). It is concluded that in patients with single-vessel disease (1) there is a high concordance between exercise echocardiography and SPECT in terms of an ischemic response, and (2) with both methods the probability of an ischemic response is related to the severity of coronary stenosis. (AM HEART J 1992;124:75.)

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Recently, cardiac imaging with echocardiography[1-11] or scintigraphy[12-24] in conjunction with exercise or pharmacologic stress has been used for the noninvasive diagnosis of coronary artery disease. However, only a few studies have been performed to compare the relative efficacy of the two tests for the diagnosis of the presence and severity of coronary artery disease, and in these studies the assessment of coronary arteriography was limited to a visual judgment.[25-27] Finally, these studies included heterogeneous groups of patients, an important limitation in determining the functional importance of coronary stenosis that could be eliminated by excluding patients with multiple-vessel disease. Therefore the aim of this study was to establish the correlation between exercise echocardiography and perfusion single-photon emission computed tomography (SPECT) in terms of "ischemic" response in a selected group of patients with single-vessel disease. In addition, we

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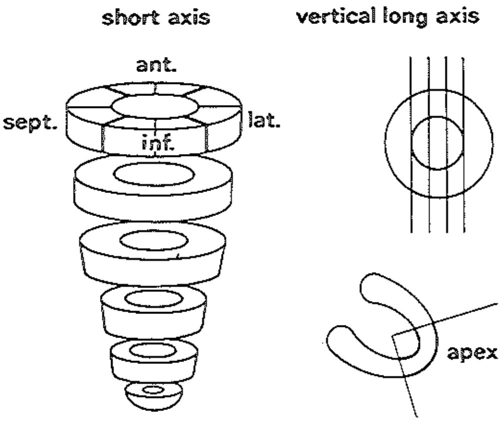

Fig. 1. Diagrammatic representation of SPECT imaging. The six short axes and three vertical long axes were used for analysis of the studies. The left ventricular wall was divided into five major regions: interventricular septum *(sept)*, anterior wall *(ant)*, lateral wall *(lat)*, inferior wall *(inf)*, and apex.

aimed to correlate the results of the two tests to the degree of the stenosis evaluated by caliper.

METHODS

From August 1989 to July 1990, 207 patients underwent simultaneous exercise echocardiography and SPECT at the Thoraxcenter. We selected 44 patients with evidence of single-vessel disease on coronary angiography performed within 2 weeks of the noninvasive tests. Inclusion criteria were (1) isolated stenosis or luminal irregularity of one coronary artery or its major branches; (2) no Q-wave myocardial infarction, cardiac surgery, valvular heart disease, or cardiomyopathy; (3) no unstable angina; and (4) good-quality exercise echocardiograms. One patient was excluded because of poor-quality echocardiograms, whereas no patient was excluded for a poor SPECT imaging. Indications for noninvasive testing included the evaluation of the physiologic significance of coronary stenosis noted on angiography (n = 15), systematic follow-up 6 months after percutaneous transluminal coronary angioplasty (n = 17), and evaluation of chest pain (n = 12). Although the patients were drawn from a large group, they represent a consecutive series meeting the above requirements.

Exercise testing. The patients performed a symptom-limited exercise test on a bicycle ergometer with stepwise increments of 20 W/min. Blood pressure was measured every 2 minutes by the cuff method. The ECG was monitored continuously (leads II, V2, and V5) and recorded (12 leads) at rest and every minute until the end of the recovery phase. A computer-assisted system (Cardiovit CSG/12; Schiller, Baar, Switzerland) analyzed the QRS complex after signal averaging. Horizontal or downsloping ST segment depression of 1 mm or greater occurring 80 msec after the J point was considered diagnostic of ischemia. Twenty-five patients exercised to 85% or greater of their expected maximal heart rate, corrected for age and gender; 36 patients reached an adequate exercise end point, defined as the development of typical angina, ST segment depression, or achievement of 85% or greater of the maximal predicted heart rate.

SPECT imaging. At peak exercise, either 370 MBq 99m-Tc-methoxyisobutyl isonitrile (MIBI) (n = 25) or 111 MBq thallium-201 (n = 19) was injected intravenously. The patient continued to exercise for another 1 to 2 minutes. When thallium-201 was administered, imaging was started within 10 minutes and repeated 4 hours after the injection. Stress MIBI SPECT images were acquired 1 hour after exercise. For resting studies, patients were reinjected with 370 MBq 99m-Tc-MIBI at least 24 hours after stress studies. All the images were acquired by Siemens Gammasonics single-head Rota Camera (Orbiter; Siemens Corp., Iselin, N.J.) equipped with 37 photomultiplier tubes, a ⅜-inch NaI crystal, and a low-energy, all-purpose collimator. Thirty-two projections were obtained, from left posterior oblique to right anterior oblique, with an acquisition time of 45 seconds per projection. The digitizing matrix (64 × 64 word mode) was selected in the midposition of the camera image, with a zoom factor of $\sqrt{2}$. A Gamma 11 computer system with a floating point processor was used to process the tomographic data. Transaxial tomograms were reconstructed with the SPETS software package (Nuclear Diagnostics AB, Hangsten, Sweden). From the three-dimensional data, oblique (short axis) and sagittal (vertical long axis) slices, perpendicular and parallel to the long axis, respectively, were reconstructed. For each study, six oblique slices were defined from the apex to the base and three sagittal slices from the septum to the lateral wall. To compare the stress and rest studies, each of the six short-axis slices was divided into eight equal segments. The septal part of the two basal slices (four segments) was not evaluated, because this region corresponds to the fibrous portion of the interventricular septum and normally exhibits reduced uptake. The apical region was assessed from the three central sagittal cross sections. A total of 47 segments per patient were analyzed. All tomographic views were reviewed in side-by-side pairs (stress and rest) by the same experienced observer, who was unaware of the patient's clinical history or the results of stress echocardiography or coronary arteriography. The myocardial uptake of radiotracer was evaluated visually with a five-point scoring method (0 = normal, 1 = slightly reduced uptake, 2 = moderately reduced uptake, 3 = severely reduced uptake, and 4 = absence of uptake). "Ischemia" was defined as a perfusion defect during exercise that partially or totally resolved at rest in at least two contiguous segments or slices. Perfusion score indexes were calculated by averaging the scores for all segments for both the stress and rest studies. An ischemic score index was generated from the difference between stress and rest indexes.

Echocardiographic imaging. Two-dimensional echocardiography was performed by an experienced cardiolo-

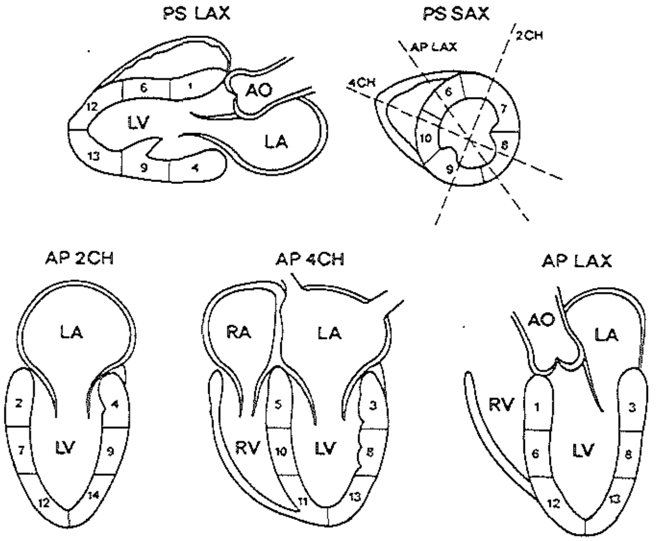

Fig. 2. Regional left ventricular wall segments in the 14-segment model. Five major regions were considered: interventricular septum (segments 1, 5, 6, and 10), anterior (segments 2 and 7), posterolateral (segments 3 and 8), inferior (segments 4 and 9), and apex (segments 11, 12, 13, and 14). *AO*, Aorta; *AP 2CH*, apical two-chamber view; *AP 4CH*, apical four-chamber view; *AP LAX*, apical long-axis view; *LA*, left atrium; *LV*, left ventricle; *PS LAX*, parasternal long-axis view; *PS SAX*, parasternal short-axis view; *RA*, right atrium; *RV*, right ventricle.

gist and recorded in the left lateral decubitus position at rest and immediately after exercise, with a commercially available system (Hewlett Packard Sonos 1000; Hewlett-Packard Co., Palo Alto, Calif.) equipped with 3.5 and 2.5 MHz transducers. All standard views were obtained at rest, and the transducer positions were marked on the chest wall to permit quick and comparable postexercise imaging. On reaching the exercise endpoint, patients resumed the resting position and stress echocardiograms were obtained. Post-exercise imaging was completed within 35 to 180 seconds. The four standard apical and parasternal views were obtained in 38 patients, whereas in 6 patients only the apical views were obtained. In four of these patients the perfusion scintigraphy was positive, whereas echocardiograms were negative for ischemia. All the studies were recorded on videotape. In addition, we employed a Nova Microsonics System (PreVue III, Nova Microsonics, Mahwah, N.J.) for digital recording and data storage. This system captured eight consecutive echocardiographic images on-line, with a sampling interval of 50 msec. One representative cardiac cycle obtained from each of four different views (generally parasternal long-axis, short-axis at papillary muscle level, and apical four- and two-chamber views) was recorded at rest and served as reference for the evaluation of subsequent changes. After exercise, the digital system allowed capture of four consecutive cardiac cycles for each view. The cycle with the highest image quality was then selected and displayed side by side with the corresponding rest cycle. Finally, two different quad-screen formats, showing the rest and stress images, were stored on a 5¼-inch double-sided, high-density floppy disk for further review as a continuous loop at different playback speeds. All the echocardiograms were reviewed, and a consensus was achieved, by two observers who had no knowledge of the SPECT results or angiographic data. The left ventricular wall was divided into 14 segments as described by Edwards et al.[26] Systolic wall thickening and inward wall motion were evaluated visually. Each segment was graded on a four-point scoring system (1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic). A new or increased wall motion abnormality after stress was considered an ischemic response. A global wall motion score index was derived by dividing the total score by the number of the segments for both rest and stress studies; an ischemic score index was calculated from the difference between stress and rest indexes. In our laboratory, interobserver and intraobserver variability for exercise echocardiography has been found to be minimal.[27]

Assignment of different left ventricular regions to specific coronary arteries. We attempted to identify the specific coronary artery involved from the location of perfusion defects and wall motion abnormalities. For this purpose, the 47 segments imaged by SPECT were combined in five regions (Fig. 1). Septal and anterior segments

Table I. Clinical data in the group of patients

Age (yr)	59 ± 9 (37-77)	
Gender (M/F) (*n*)	35/9	
Previous non-Q-wave myocardial infarction (*n*)	16	
Radiotracer (*n*)	201-Tl 19/MIBI 25	
β-Blocker therapy (*n*)	15	
≥85% predicted maximal heart rate (*n*)	25	
Coronary artery disease (*n*)	*% Diameter stenosis*	
	≥50	<50
LAD	15	6
RCA	8	5
LC	7	3

LAD, Left anterior descending artery; *RCA*, right coronary artery; *LC*, left circumflex artery.

were considered to correspond to the left anterior descending artery, inferior segments to the right coronary artery, and lateral segments to the left circumflex artery. When perfusion defects overlapped these boundaries, defects found primarily in one territory that did not extend significantly over the border of another territory were considered to represent one lesion. The 14 echocardiographic segments were similarly categorized: anterior (segments 2 and 7), lateral (segments 3 and 8), inferior (segments 4 and 9), interventricular septum (segments 1, 5, 6, and 10), and apex (segments 11, 12, 13, and 14) (Fig. 2). The interventricular septum and anterior wall were attributed to the left anterior descending artery distribution, the lateral wall to the left circumflex artery, and the inferior wall to the right coronary artery. For both methods the attribution of the apex abnormalities was flexible, depending on coexistent abnormalities in adjacent regions.

Coronary arteriography. Selective coronary arteriography was performed in multiple views according to the Judkins technique. Coronary cineangiograms were analyzed with a personal computer–based coronary analysis system with a manual caliper program in its basic configuration. For this purpose, the cinefilm was mounted on a standard Tagarno 35 CX projector (Tagarno, Horsens, Denmark) with built-in video camera. A selected cineframe was then converted into video format, digitized at a resolution of 512 by 512 by 8 bits, and displayed on a video monitor. For calibration, a region of interest around the catheter tip was selected with the mouse of the system, magnified twofold with linear interpolation, and displayed on the video monitor for subsequent measurements. Next the user indicated with the mouse three pairs of points at the sides of the magnified catheter segment. The average value of the measured width expressed in pixels was compared with its true size (in millimeters), resulting in a calibration factor in millimeters/pixel. Then the arterial segment to be analyzed was magnified twofold and interpolated linearly, the user defined the obstruction, and the reference diameter stenosis was calculated. The percentage stenosis was obtained by averaging the values obtained in at least two views including the oblique views. The length of the stenosis was not taken into account in this study. A stenosis was considered "significant" when it was equal to or greater than 50%.

Statistical analysis. Data are presented as mean values ± SD, when appropriate. Specificity, sensitivity, and predictive accuracy relied on standard definitions. The χ^2 test and Fisher's exact test were used to compare differences between proportions. Correlation between ischemic perfusion, wall motion score indexes, and stenosis severity were sought by regression analysis. The Student *t* test was used for analysis of continuous data. A $p < 0.05$ was considered statistically significant.

RESULTS

Some baseline clinical data and the findings on coronary arteriography are reported in Table I.

Exercise echocardiography and SPECT results. The results of exercise ECG, echocardiography, and SPECT, according to the location of wall motion abnormalities and perfusion defects, both at rest and after stress, and the angiographic data are displayed in Table II. "Fixed" perfusion defects without corresponding wall motion abnormalities at rest were found in seven patients; in five patients a reversible perfusion defect in the same area was also present on thallium-201 scintigraphy. In two patients wall motion abnormalities at rest without worsening after stress were detected in the territory supported by a coronary stenosis with a diameter greater than 50%, in the presence of normal perfusion.

When the positivity of stress echocardiograms and SPECT was defined as new wall motion abnormalities or transient perfusion defects, the concordance between the two tests was 79%. Twenty patients (45%) had a concordant positive stress echocardiogram and SPECT, and 15 (34%) had concordant negative test results. Seven patients (16%) had positive SPECT and negative echocardiograms. In four of these patients only apical echocardiographic views were obtained. Right coronary artery stenosis was found in four and left circumflex stenosis in three of these patients. Compared with patients with positive results in both tests, in these seven patients the time of recording the first and last echocardiographic images from the end of exercise was longer (53 ± 45 vs 24 ± 10 seconds, [$p = 0.01$]; 121 ± 43 vs 85 ± 29 seconds [$p = 0.05$]), but the mean ischemic perfusion score index was not different (0.25 ± 0.15 vs 0.37 ± 0.24 seconds; difference not significant). Only two patients (5%) had positive echocardiograms with negative SPECT; both had left anterior descending artery stenosis (48% and 67% diameter stenosis, respectively).

The overall sensitivity, specificity, and diagnostic

Table II. Results of exercise echocardiography and SPECT with correlative findings on coronary angiography

				Exercise test		*SPECT*		*Echocardiography*		*Angiography*	
Pt.	*Isotope*	*MI*	*bB*	*AP*	*ST*	*Rest*	*Stress*	*Rest*	*Stress*	*Vessel*	*DSt (%)*
1	MIBI	+	+	–	+	–	LAD	–	LAD	LAD	100
2	MIBI	–	–	–	+	–	LAD	–	LAD	LAD	100
3	MIBI	+	–	–	+	LC	LC	–	LC	LC	100
4	MIBI	+	+	–	–	LC	LC	LC	–	LC	87
5	201-Tl	+	+	+	+	–	LC	–	RCA	LC	87
6	MIBI	+	+	–	–	–	LAD	–	LAD	LAD	80
7	MIBI	–	–	–	+	–	RCA	–	RCA	RCA	80
8	201-Tl	–	+	+	+	–	LAD	–	LAD	LAD	77
9	201-Tl	–	–	–	+	–	LC	–	LC	RCA	75
10	201-Tl	+	+	+	+	–	LC	–	LC/LAD	RCA	74
11	201-Tl	+	–	–	+	–	LAD	–	LAD	LAD	74
12	201-Tl	–	–	–	+	RCA	RCA	–	LC	RCA	73
13	201-Tl	–	–	–	–	–	–	RCA	–	RCA	70
14	MIBI	–	–	+	+	–	–	–	LAD	LAD	67
15	MIBI	–	–	–	+	–	LAD	–	LAD	LAD	65
16	201-Tl	+	+	–	+	LAD	LAD	LAD	LAD	LAD	64
17	201-Tl	+	–	–	+	–	–	LC	–	LC	62
18	201-Tl	–	–	+	+	LC	LC	–	LC	LC	61
19	201-Tl	+	–	+	+	LAD	LAD	–	LAD	LAD	61
20	201-Tl	–	+	–	–	RCA	RCA	–	RCA	RCA	59
21	MIBI	+	+	–	–	LAD/RCA	RCA	LAD	–	RCA	59
22	201-Tl	–	+	–	–	–	RCA	–	–	LC	59
23	201-Tl	+	–	–	–	–	RCA	–	–	RCA	58
24	201-Tl	–	+	–	–	–	–	–	–	LAD	58
25	201-Tl	+	+	–	–	LAD	LAD	–	LAD	LAD	57
26	MIBI	–	–	–	+	LAD	–	LAD	–	LAD	55
27	MIBI	–	–	–	+	–	LAD	–	LAD	LAD	54
28	MIBI	–	–	–	–	–	RCA	–	LC	LC	53
29	201-Tl	–	–	+	+	–	–	–	–	LAD	52
30	MIBI	+	–	–	–	LAD	–	LAD	–	LAD	52
31	MIBI	–	–	+	–	–	LAD/RCA	–	LAD	LAD	49
32	MIBI	–	–	–	–	–	–	–	LAD	LAD	48
33	MIBI	–	+	+	–	–	–	–	–	LAD	48
34	MIBI	–	–	–	+	–	–	–	–	LAD	47
35	MIBI	+	+	–	–	–	RCA	–	–	LC	43
36	MIBI	–	–	–	–	–	–	–	–	LC	41
37	201-Tl	–	+	–	–	–	–	–	–	LAD	40
38	201-Tl	–	–	+	–	–	–	–	–	LAD	37
39	MIBI	–	–	–	–	–	–	–	–	RCA	35
40	MIBI	–	–	–	–	–	–	–	–	LC	34
41	MIBI	–	–	–	–	–	–	–	–	RCA	32
42	MIBI	+	–	–	–	RCA	–	–	–	RCA	30
43	MIBI	–	–	–	–	–	LAD/RCA	–	–	RCA	22
44	MIBI	–	–	–	–	–	RCA	–	–	RCA	21

AP, Angina pectoris; *bB*, β-blocker therapy; *DSt*, diameter stenosis; *MI*, previous non-Q-wave myocardial infarction; *ST*, ST segment depression; *MIBI*, methoxyisobutyl isonitrile; *Tl*, thallium; remaining abbreviations as in Table I. For both SPECT and echocardiography, the site of perfusion defects or wall motion abnormalities is assigned to the corresponding specific coronary artery, as described in the text.

accuracy for detecting coronary artery disease (with a diameter stenosis ≥50% as "gold standard") by ECG, echocardiographic, and scintigraphic changes are summarized in Table III. The trend toward higher sensitivity of SPECT was counterbalanced by an opposite trend in specificity, so predictive accuracy was the same. No significant difference in the overall sensitivity and specificity was found when patients were analyzed separately according to the attainment of 85% or greater of the maximal predicted heart rate, the presence of previous non-Q-wave myocardial infarction, β-blocker therapy, or the radiotracer used.

The ability of exercise echocardiography and

Table III. Overall sensitivity, specificity, and diagnostic accuracy for detecting coronary artery disease with a diameter stenosis of 50% or greater

	Sensitivity		*Specificity*		*Diagnostic accuracy*	
	%	*n*	%	*n*	%	*n*
ECG	63	19/30	93	13/14	72	32/44
Echocardiography						
NWMA	66	20/30	85	12/14	72	32/44
NWMA or resting WMA	86	26/30	85	12/14	86	38/44
SPECT						
TPD	76	23/30	71	10/14	75	33/44
TPD or resting PD	83	25/30	64	9/14	77	34/44

NWMA, New wall motion abnormalities; *TPD*, transient perfusion defects.

Table IV. Sensitivity and specificity of exercise echocardiography (new wall motion abnormalities) and SPECT (transient perfusion defects) for detection of stenosis of 50% or greater for individual coronary arteries

	Echocardiography				*SPECT*			
	Sensitivity		*Specificity*		*Sensitivity*		*Specificity*	
	%	*n*	%	*n*	%	*n*	%	*n*
LAD	73	11/15	89	26/29	66	10/15	93	27/29
RCA	25	2/8	97	35/36	62	5/8	83	30/36
LC	42	3/7	91	34/37	57	4/7	94	35/37
RCA/LC	60	9/15	100	29/29	86	13/15	86	25/29

Abbreviations as in Table I.

SPECT to identify the location of individual coronary artery lesions is displayed in Table IV for each major coronary artery and for the left circumflex and right coronary arteries combined. Among 15 patients with left circumflex or right coronary artery stenosis of 50% or greater, the site of the stenosis was erroneously attributed to the contiguous vascular territory in seven (in four patients by echocardiography and four patients by SPECT). The results are much better when the territories of the right coronary artery and left circumflex artery were merged, partially avoiding the problem of their overlap.

Correlation of exercise echocardiography and SPECT with the severity of coronary stenosis. The effect of severity of stenosis on the detection rate of lesions is displayed in Fig. 3. From Fig. 3 it is seen that the prevalence of an ischemic response was related strictly to the severity of the coronary stenosis ($p < 0.001$). All the lesions with a diameter stenosis greater than 70% were identified by SPECT, whereas echocardiography identified 11 of 12 patients (100% vs 91%: difference not significant). Of the 18 patients with coronary stenoses of intermediate severity (diameter stenosis 50% to 70%), scintigraphic ischemia was present in 11 and echocardiographic ischemia in 9 (61% vs 50%; difference not significant). In the group with nonsignificant coronary stenosis, four patients had positive SPECT and two had positive echocardiographic results (28% vs 14%; difference not significant). The two patients with false-positive responses on echocardiography had a left anterior descending artery stenosis of 49% and 48%, and in one patient a transient perfusion defect was also found.

The relationship between ischemic perfusion score index and ischemic wall motion score index is shown in Fig. 4. Despite the different left ventricular segmentation and scale grading used, a good correlation between the two ischemic score indexes was found ($r = 0.709$; $p < 0.001$). The relationships between the amount of myocardium at risk (as assessed by the ischemic score indexes) and the severity of coronary artery stenosis (expressed as % diameter stenosis) are represented in Figs. 5 and 6. Moreover, in patients with either a positive exercise echocardiography or SPECT result, the mean value of ischemia index was higher in patients with 70% or greater than in patients with less than 70% diameter stenosis (0.50 ± 0.21 vs 0.27 ± 0.10 [$p < 0.005$]; 0.46 ± 0.27 vs 0.24 ± 0.12 [$p < 0.01$], respectively).

DISCUSSION

In recent years, exercise echocardiography has been proposed as a feasible, safe, and low-cost alternative to scintigraphy.[1-9] However, in most of these studies the results of exercise echocardiography have been validated by visual estimates of severity of stenosis. There are very few studies addressing the comparative value of the two tests in the diagnosis of myocardial ischemia and coronary artery disease.[25-27] This is the first study in which exercise echocardiography and SPECT were applied simultaneously and their results compared with the percent diameter stenosis assessed semiquantitatively. The main results of this study can be summarized as follows: (1) The agreement between exercise echocardiography and perfusion SPECT imaging (in terms of response and severity of ischemia) is very high. (2) The probability of an ischemic response on exercise echocardiography or SPECT is dependent on the severity of coronary stenosis when assessed as percent diameter stenosis; particularly, a negative test result is highly predictive of a diameter coronary stenosis less than 70%, with both methods. (3) There is a fair correla-

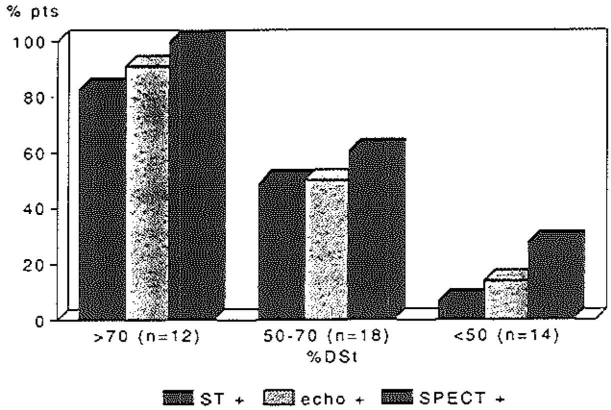

Fig. 3. Prevalence of a positive results on exercise electrocardiography *(ST)*, echocardiography *(echo)*, or SPECT in subgroups of patients with different severity of coronary artery stenosis *(% DSt)*.

tion between the severity of coronary artery stenosis and the severity of myocardial ischemia.

We have already assessed the diagnostic value of exercise echocardiography and perfusion 99m-Tc-MIBI SPECT in the detection of coronary artery disease in a group of patients with normal ECG at rest.[27] However, in that study patients with multiple-vessel disease and patients with stenotic lesions of less than 50% were also included. In contrast to our previous work, this study includes only patients with lesions limited strictly to one major vessel, and the severity of the lesion was graded on a continuous scale by the caliper technique.

The overall sensitivity and specificity of both exercise echocardiography and SPECT are apparently not optimal. However, we like to underscore that our study group included only patients with single-vessel disease, and most were taking medication, both factors reducing the sensitivity of any diagnostic test compared with patients with multiple-vessel disease or not taking medication. Also the specificity could appear suboptimal. However, we should remember that this study included patients with a continuous spectrum of coronary stenoses and we dichotomized the group according to a cutoff of 50% diameter stenosis. It is therefore likely that some patients with angiographic "subcritical stenosis" were uncorrectly defined as having false-positive results, if the hemodynamic sequela of such a lesion was greater than predicted based on its angiographic appearance.

In this study the disagreement between exercise echocardiography and SPECT was infrequent and mostly the result of patients with positive SPECT

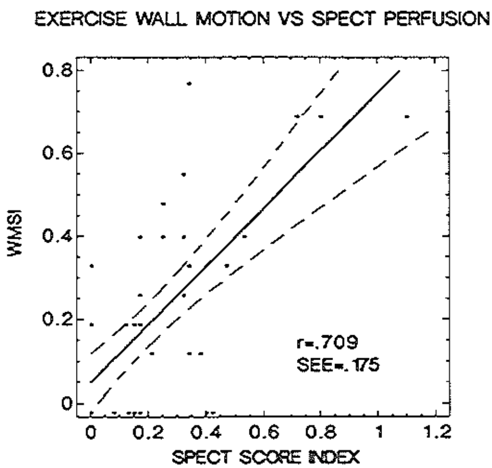

Fig. 4. Correlation between echocardiographic and scintigraphic indexes of exercise-induced myocardial ischemia. A significant correlation was observed ($p < 0.001$). *WMSI*, wall motion score index.

and negative echocardiograms (Fig. 3). This finding could be related to multiple factors such as (1) the site and extent of myocardial ischemia; (2) the rapid recovery of myocardial ischemia after termination of exercise; and (3) maldistribution of flow, rather than true ischemia. It has been reported that wall motion abnormalities can persist for an extended period of time[3]; however, some individuals show a very rapid recovery of the wall motion changes after bicycle ex-

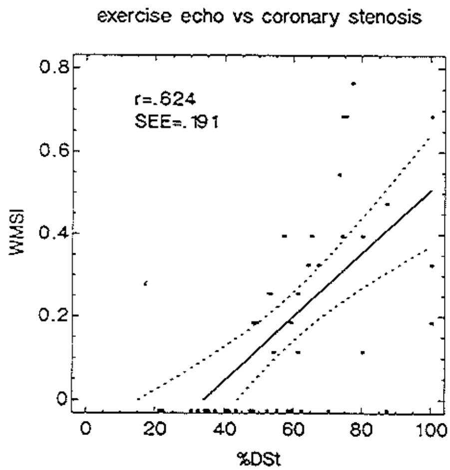

Fig. 5. Correlation between ischemic wall motion score index *(WMSI)* and stenotic percent diameter *(%DSt)*. A significant correlation was found ($p < 0.001$).

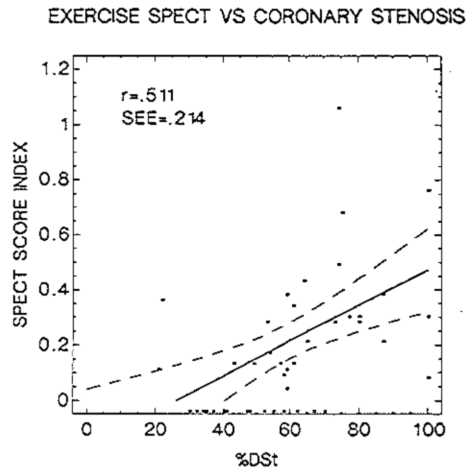

Fig. 6. Correlation between ischemic perfusion score index and stenotic percent diameter *(%DSt)*. A significant correlation was found ($p < 0.001$).

ercise. Therefore postexercise imaging will fail to identify some patients with a limited amount of ischemic myocardium who exhibit rapid resolution of exercise-induced wall motion abnormalities. Addition of echocardiographic imaging at peak exercise could enhance the sensitivity for the detection of coronary artery disease with exercise echocardiography.[29,30] Our findings suggest that inability to record short-axis views at mid-papillary muscle level or a delay in acquiring postexercise imaging play a critical role in determining these false-negative echocardiographic study results. These patients tended to have a smaller ischemic zone than had patients with positive results to both tests. Accordingly, maldistribution of flow without real ischemia is unlikely to explain all the discrepancies between echocardiographic and scintigraphic findings.

Comparison of the extent of ischemic region with severity of coronary stenosis. Analysis of scintigraphic and echocardiographic images showed that the amount of jeopardized myocardium was correlated directly when evaluated by the two ischemic indexes, despite the different left ventricular segmentation and scoring system used. With both methods, the extent and severity of myocardial ischemia was greater in patients with severe (>70%) than in patients with less severe (<70%) coronary artery stenosis; however, in the individual patient the score is not helpful to predict the severity of coronary stenosis, because of a considerable scatter of data when percent diameter stenosis is related to ischemic score indexes. This is not an unexpected finding, because the population in this study represents a broad spectrum of single-vessel disease, with coronary artery stenosis in different vessels and different sites of the same vessel.

Limitations of the study. A potential limitation of this study is that two different radiotracers were used for perfusion studies. It is well known that thallium-201 imaging can result in fixed perfusion defects in the absence of scar, caused by late redistribution[31]; this could decrease the prevalence of ischemic responses. In this study the six patients with fixed defects on thallium-201 scintigraphy also had an associated transient defect in the same area; because our criterion for positivity of SPECT was the presence of transient defects, all these cases were considered positive independently from the fixed defects. Another limitation is the result of the visual assessment of both perfusion and echocardiographic studies. In this regard, although quantitative analysis of SPECT is gaining acceptance, such analysis applied to stress echocardiography is not yet a standardized procedure.

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CHAPTER 5.

Exercise echocardiography and single photon emission computed tomography in patients with left anterior descending coronary artery stenosis.

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Exercise echocardiography and single photon emission computed tomography in patients with left anterior descending coronary artery stenosis

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Abstract

To compare the diagnostic value of exercise echocardiography and perfusion single photon emission computed tomography (SPECT) in the detection of the presence and the severity of coronary artery disease, we studied 21 patients with isolated stenosis of different degree of the left anterior descending artery. Both echocardiography and SPECT were performed in conjunction with the same symptom-limited bicycle exercise test. Positivity of the test was based on the presence of exercise-induced wall motion abnormalities and transient perfusion defects, respectively. For both tests, an 'ischemic' score was derived, as index of extent and severity of myocardial ischemia. Coronary arteriography was evaluated by caliper.

The agreement between exercise echocardiography and SPECT for the presence of coronary artery disease was 90%; the discordance was due to two patients with positive echocardiography and negative SPECT. A good correlation between ischemic wall motion and perfusion score indices was found ($r = 0.78$, $p < 0.0001$. Moreover, the percent diameter stenosis was well correlated with both ischemic indices ($r = 0.75$, $p < 0.0001$; $r = 0.67$, $p < 0.001$, respectively). In patients with a positive test, the mean value of ischemic wall motion score index was higher in patients with a diameter stenosis $\geq 70\%$ than in patients with a diameter stenosis $< 70\%$ (0.59 ± 0.19 vs 0.29 ± 0.12, $p < 0.01$); a similar trend was found for ischemic perfusion score index (0.51 ± 0.35 vs 0.27 ± 0.12, ns).

The results of this study indicate that in patients with single vessel disease of left anterior descending artery exercise echocardiography and SPECT give the same information on the presence, the extent and the severity of myocardial ischemia.

Introduction

Exercise electrocardiography and myocardial perfusion scintigraphy are the most common non-invasive diagnostic tests in patients with suspected coronary artery disease [1–7]. In the last few years, exercise echocardiography is emerging as a promising alternative for assessing the functional severity of coronary stenoses [8–11]. However, few studies have been addressed to compare the relative diagnostic efficacy of the two imaging tests [12–14]. Furthermore, no study has been designed so far to explore the relation between the results of exercise echocardiography and exercise perfusion scintigraphy (when simultaneously applied) in patients with coronary stenosis of different severity. In most clinical studies, the visual assessment of coronary stenoses has been used as 'gold standard' for assessing the diagnostic efficacy of non-invasive tests.

Accordingly, we wanted to assess the diagnostic value of simultaneous exercise echocardiography and perfusion single photon emission computed tomography (SPECT) in a homogeneous group of patients with isolated left anterior descending coronary artery stenosis, quantitatively assessed.

Study group

From july 1989 to august 1990, 221 patients primarily referred for perfusion scintigraphy underwent simultaneous exercise echocardiography and SPECT at the Thoraxcenter. From this large group we selected all the patients who fulfilled the following requirements: 1) isolated narrowing limited to the left anterior descending artery on coronary arteriography performed within two weeks of the non invasive test; 2) no ECG evidence of previous transmural myocardial infarction; 3) no previous cardiac surgery; 4) no evidence of cardiomyopathies, congenital or acquired valvular heart disease. Twenty-one patients comprised the study group representing a consecutive series meeting the above requirements; 17 were men and 4 were women. Their mean age ranged from 37 to 77 years (mean 59 ± 11 years). Seven patients had a documented previous non-Q wave myocardial infarction. At the time of the tests, betablockers were being taken by 8 patients.

Methods

All patients underwent a symptom limited upright bicycle ergometry with stepwise increments of 20 Watts each minute. ECG was continuously monitored (leads II, V2, V5) and recorded every minute (12-lead). The level of the ST segment was calculated by a signal averaged computerized system (Cardiovit CSG/12, Schiller). A ≥ 1 mm horizontal or downsloping ST segment depression occurring 80 msec after the J point was considered ischemic. Seventeen patients reached an adequate exercise end-point, defined as the development of typical angina pectoris, ischemic ST segment depression, or achievement of ≥ 85% of their maximal predicted heart rate.

SPECT imaging

At peak exercise, either 370 MBq of 99 m-Tc-metoxy isobutyl isonitrile (MIBI) (n = 12) or 111 MBq of 201-thallium (n = 9) was injected in an antecubital vein. Patients continued to exercise for another one to two minutes. Then, the protocol was different, according to the different radiotracer used. When 201-thallium was administered, stress imaging started within 10 minutes of the termination of exercise and redistribution images were acquired 4 hours after the injection. When MIBI was used, stress images were acquired one hour after exercise: for resting studies, patients were reinjected with 370 MBq of MIBI at least 24 hours after the stress studies.

All the images were acquired by a Siemens Gammasonics single head Rota Camera (Orbiter) equipped with 37 photomultiplier tubes, a 3/8 inch NaI crystal and a low-energy, all-purpose collimator. Thirty-two projections were obtained (180° scanning, from left posterior oblique to right anterior oblique projection) with an acquisition time of 45 sec per projection. The digitizing matrix (64 × 64 word mode) was selected in the mid portion of the camera image by using a zoom factor $\sqrt{2}$. Tomographic data were reconstructed with the SPETS package (Nuclear Diagnostic AB, Hagsten, Sweden). The direction of left ventricular long axis was determined from two orthogonal views (anterior and lateral): oblique slices (short axis) and sagittal slices (vertical long axis), perpendicular and parallel to the long axis respectively, were reconstructed. For each patients, six oblique (short axis) slices were defined from the apex to the base, and three sagittal slices from septum to the lateral wall.

To compare exercise and reperfusion studies, the short axis and the sagittal slices were displayed as pairs and interpreted by the same experienced observer, who was unaware of clinical data, echocardiographic and angiographic results. In our center, simultaneous scintigraphic and echocardiographic studies are always interpreted and scored without knowledge of other data. Each short axis slice was divided into 8 equal-sized regions; the septal part of the two upper slices (4 segments) was not evaluated, since this portion corresponds to the fibrous interventricular septum and may result in reduced uptake. The apical region was evaluated from the three central sagittal cross section, yelding a total of 44 + 3 = 47 segments per patient study. The myocardial uptake of the radiotracer was visually graded for each segment with a 5-point scale (0 = normal, 1 = slightly reduced uptake, 2 = moderately reduced uptake, 3 = severely reduced uptake, 4 = 'absence' of uptake). An 'ischemic' response was defined as transient perfusion defects in at least two contiguous segments and/or slices. Perfusion score indices were then calculated by averaging the scores for all segments, both in the post-exercise and in the rest studies. An 'ischemic' perfusion score index was derived by the difference between stress and rest indices, giving an idea on both extent and severity of myocardial ischemia.

Exercise echocardiography

All echocardiograms were performed by a cardiologist, using either a 3.5 or 2.5 MHz transducer and a commercially available wide angle phased array system (Hewlett Packard, Sonos 1000). Standard parasternal long- and short-axis views and apical two and four chamber views were recorded at rest with the patient in the left lateral position. Multiple apical views, including the apical long-axis view, were used instead of parasternal views when the latter gave poor image quality. After reaching the exercise end point, the patients were immediately placed in the same left lateral position and the stress echocardiograms were obtained in the same four views. The rest and stress images were recorded on videotape and were also digitized on line using a Nova Microsonics PreVue III system. This system was set up to record at rest one representative cardiac cycle obtained from 4 different views. After exercise, 4 consecutive cardiac cycles for each view were captured; the cycle with the highest image quality was then selected and displayed side-by-side with the corresponding rest cycle. Two different quad-screen formats, showing the rest and stress images, were finally stored in a 5 1/4 inch double-side high-density floppy disk.

All echocardiograms were reviewed on floppy disk as a continuous loop at different playback speeds by two observers who were unaware of the results of exercise test, scintigraphic data or coronary arteriography. For purpose of analysis, left ventricular wall was divided into 14 segments [15]. Both systolic wall thickening and inward wall motion were visually evaluated; each segment was graded with a 4-point scale (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic). An ischemic response was defined as a wall motion abnormality in one or more segments which were normal at rest, or a worsening of wall motion in one or more segments which were hypokinetic at rest. A wall motion score index was derived, for both rest and stress studies, by dividing the total score by the number of the segments. An 'ischemic' wall motion score index was then calculated from the difference between stress and rest indices. Accordingly, an ischemic score by 0 was associated with no evidence of stress-induced myocardial ischemia. In our laboratory, inter-and intra-observer variability for stress echocardiography has been found to be minimal [14].

Assignment of different left ventricular regions to specific coronary arteries

To assign the vascular territories of the different coronary arteries, both the 47 segments imaged by SPECT and the 14 segments imaged by echocardiography were combined in the same corresponding ventricular regions, denoted as anterior, posterolateral, inferior, interventricular septum, and apex. The interventricular septum and the apex were attributed to the left anterior descending artery distribution; the lateral wall to the left circumflex artery; the inferior wall to the right coronary artery.

Coronary arteriography

Coronary arteriography was performed using the Judkins technique. Coronary cineangiograms were analyzed with a PC-based coronary analysis system with a manual caliper program in its basic configuration, developed in our center [16]. For this purpose, the cinefilm was mounted on a standard Tagarno 35 CX projector with built-in video camera. A selected cineframe was then converted into video format, digitized at a resolution of 512 × 512 × 8 bits and displayed on a video monitor. For calibration, a region-of-interest around the catheter tip was selected with the mouse of the system, magnified two-fold with linear interpolation and displayed on the video monitor for subsequent measurements. Next, the user indicated with the mouse three pairs of points at the sides of the magnified catheter segment. The average value of the measured width expressed in pixels was compared with its true size (in mm), resulting in a calibration factor in mm/pixel. Then, the arterial segment to be analysed was magnified two-fold and linearly interpolated, and the user defined the obstruction and reference diameters. From these absolute values, percent diameter stenosis was calculated.

Table 1. Exercise echocardiography and SPECT with the coronary angiography findings in the study group.

Pt	A/G	MI	bB	ANGIO	ECHO		SPECT		ISCHEMIC INDICES		EXERCISE TESTING			RADIOTRACER
					rest	stress	rest	stress	echo	spect	ap	st	end-point	
1)	56/M	+	+	100%	–	LAD	–	LAD	.71	.80	–	+	+	MIBI
2)	40/M	–	–	100%	–	LAD	–	LAD	.35	.34	–	+	+	MIBI
3)	49/M	+	+	80%	–	LAD	–	LAD	.42	.32	–	–	+	MIBI
4)	63/M	–	+	77%	–	LAD	–	LAD	.79	.34	+	+	+	201-TI
5)	55/M	+	–	74%	–	LAD	–	LAD	.71	1.10	–	+	+	201-TI
6)	77/M	–	–	67%	–	LAD	–	–	.35	0	+	+	+	MIBI
7)	61/M	–	–	65%	–	LAD	–	LAD	.42	.25	–	+	+	MIBI
8)	66/M	+	+	64%	LAD	LAD	LAD	LAD	.35	.47	–	+	+	201-TI
9)	37/M	+	–	61%	–	LAD	LAD	LAD	.14	.38	+	+	+	201-TI
10)	43/M	–	+	58%	–	–	–	–	0	0	–	–	–	201-TI
11)	51/M	+	+	57%	–	LAD	LAD	LAD	.42	.17	–	–	+	201-TI
12)	75/M	–	–	55%	LAD	–	LAD	–	0	0	–	+	+	MIBI
13)	71/F	–	–	54%	–	LAD	–	LAD	.14	.21	–	+	+	MIBI
14)	64/F	–	–	52%	–	–	–	–	0	0	+	+	+	201-TI
15)	64/M	+	–	52%	LAD	–	LAD	–	0	0	–	–	+	MIBI
16)	68/M	–	–	49%	–	LAD	–	LAD/RCA	.21	.17	+	–	+	MIBI
17)	64/M	–	–	48%	–	LAD	–	–	.21	0	–	–	+	MIBI
18)	44/F	–	+	48%	–	–	–	–	0	0	+	–	–	MIBI
19)	67/M	–	–	47%	–	–	–	–	0	0	–	+	+	MIBI
20)	61/M	–	+	40%	–	–	–	–	0	0	–	–	–	201-TI
21)	65/F	–	–	37%	–	–	–	–	0	0	+	–	–	201-TI

A/G = Age/gender; MI = previous non-Q wave myocardial infarction; bB = betablocker therapy; Angio = percent diameter stenosis on coronary arteriography; ap = angina pectoris, st = ischemic ST segment changes; end-point = achievement of an adequate end-point.
The results of exercise echocardiography and SPECT are expressed as specific coronary arteries attributed to wall motion abnormalities or perfusion defects. LAD = left anterior descending artery; RCA = right coronary artery.

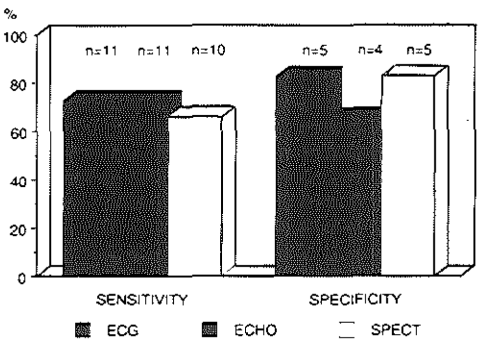

Fig. 1. Sensitivity and specificity of exercise ECG, echocardiography (ECHO) and SPECT for the detection of left anterior descending coronary artery disease (diameter stenosis ≥ 50%). Numbers on the top of the bars represent absolute values.

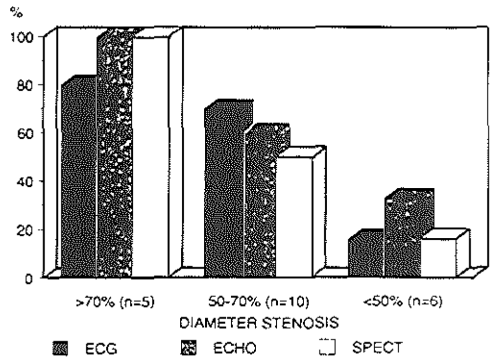

Fig. 2. Prevalence of a positive result on exercise ECG, echocardiography (ECHO) and SPECT according to the different severity of left anterior descending coronary artery stenosis.

Results

Some clinical data, the results of exercise ECG, echocardiography and SPECT, and the findings on coronary arteriography are reported in Table 1.

Sensitivity and specificity of exercise ECG, echocardiography and SPECT for the diagnosis of coronary artery disease (defined as % diameter stenosis ≥50) are represented in Fig. 1. ST segment depression was present in 11 patients with and in 1 patient without coronary artery disease. Transient wall motion abnormalities were detected in 13 patients; in 11 of them a diameter stenosis ≥50% was found. The other two patients had a diameter stenosis of 49% and 48%, respectively. All patients with a negative echocardiography had a diameter stenosis <60%.

Transient scintigraphic perfusion defects were found in 11 patients: ten of them had a diameter stenosis ≥50%. The other patients had a diameter stenosis of 49% and concordant stress induced wall motion abnormalities.

The relation between the results of the tests and the severity of coronary artery disease is shown in Fig. 2. The prevalence of a positive exercise echocardiography or SPECT is related to the degree of the stenosis: all the patients with a diameter stenosis >70% had both positive exercise echocardiography and SPECT; in the 10 patients with a diameter stenosis between 50 and 70%, exercise echocardiography and SPECT were positive in 6 and in 5 patients, respectively; and in the group with a diameter stenosis <50%, two patients were positive on echocardiography and one patient on SPECT. The incidence of ST segment depression was more 'uniform', while the distribution of angina pectoris during the test was unpredictable.

The agreement between exercise echocardiography and SPECT for the presence of coronary artery disease is represented in Fig. 3. There was an overall good agreement between the two tests (19/21 patients, 90%). Of the 8 patients with both tests negative, 4 did not achieve an adequate exercise end-point. The disagreement was due to two patients who had a positive exercise echocardiography without transient perfusion defects on SPECT.

Assuming that ischemic score indices represent the amount of myocardium at risk, we compared wall motion and perfusion score indices each other and with the diameter stenosis. Although the different left ventricular wall segmentation and the different score system we used, a good correlation between the two indices was found ($r = .78$, $p < 0.0001$). Moreover, the % diameter stenosis was well correlated with both wall motion and perfusion ischemic score indices ($r = .75$, $p < 0.0001$; $r = .67$, $p < 0.001$, respectively).

Among patients with a positive test, ischemic wall motion score index was higher in patients with

		ECHO +	ECHO -
SPECT	+	11	0
	-	2	8

Fig. 3. Agreement between exercise echocardiography and SPECT in the study group. + = positive result; – = negative result.

diameter stenosis ≥ 70% than in patients with diameter stenosis < 70% (0.59 ± 0.19 vs 0.29 ± 0.12, $p < 0.01$); a similar trend was found for ischemic perfusion score index, although the difference was not statistically significant (0.51 ± 0.35 vs 0.27 ± 0.12, ns) (Fig. 4).

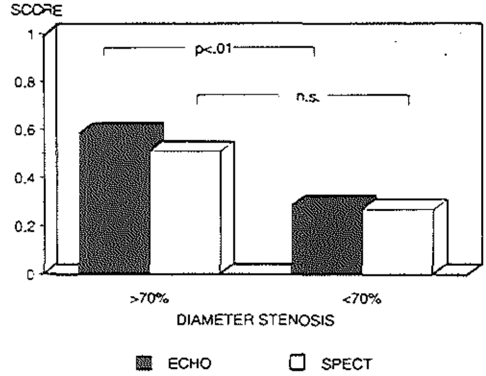

Fig. 4. Mean wall motion (ECHO) and perfusion (SPECT) ischemia score indices in patients with positive test and different degree of coronary artery stenosis.

Discussion

The purpose of this study was to compare exercise echocardiography and perfusion SPECT in a group of patients with left anterior descending coronary arterial stenoses. In recent years, exercise echocardiography has been proposed as a feasible and low-cost alternative technique to scintigraphy for the diagnosis of coronary artery disease [8–11]. However, there are very few studies addressing the comparative value of the two tests for the diagnosis of the presence and the severity of coronary artery disease, and in these studies the assessment of coronary arteriograms was limited to a visual judgement [12–14]. We have already compared the results of exercise echocardiography and perfusion SPECT in patients with suspected coronary artery disease and normal ECG at rest [14]; we found a very good agreement between the two tests for the detection of left anterior descending artery stenoses visually evaluated.

The main features of the present study are: a) the homogeneous group of patients with single-vessel disease of proximal or mid left anterior descending artery; 2) exercise echocardiography and SPECT simultaneously performed; 3) analysis of coronary lesions by caliper technique.

The results indicate an excellent agreement between exercise echocardiography and scintigraphy for the diagnosis of the presence of 'significant' coronary disease and for the severity of myocardial ischemia. In particular, analysis of echocardiograms and SPECT showed a more extensive and severe new wall motion abnormalities and transient perfusion defects in patients with diameter stenosis > 70%, compared to patients with less severe stenoses (Fig. 4); however, in the individual patient the score is not helpful to predict the severity of coronary stenosis, due to the considerable overlap of the values.

Consistent with previous scintigraphic and echocardiographic studies [17–20], sensitivity was highest in patients with more severe lesions, of 70% or more, confirming that the prevalence of an ischemic response is primarily related to the severity of coronary stenosis. Based on our previous experience [12–14, 21], these positive results cannot be extended to patients with disease of left circumflex or right coronary artery, in which the sensitivity of exercise echocardiography is slightly lower than that obtained by SPECT.

Limitations of the study

In this group of patients the usual antianginal therapy was not discontinued; this could affect the assessment of 'true' sensitivity and specificity of the tests. In particular, 4 of the 8 patients with both tests negative did not reach an adequate exercise end-point, and 3 of them were on betablocker therapy. However, the aim of this study was not to assess the physiologic significance of a coronary stenosis. Rather, we wanted to compare exercise echocardiography an SPECT for the detection of myocardial ischemia in a group of patients primarily referred for perfusion scintigraphy, conditional to their medical treatment.

Another potential limitation of this study is due to the different radiotracers used for SPECT studies. The presence of a 'fixed' perfusion defect on 201-thallium imaging could be due to late redistribution, indicating ischemia rather than scar [22]. This could decrease the prevalence of an ischemic response. In the present study, 3 patients had a fixed defect on 201-thallium SPECT, but all of them had also a reversible defect in the same area. Since positivity of SPECT was based on the presence of reversible defects, these 3 patients were considered positive, independently from the fixed defects.

Clinical implications

The results of this study suggest that exercise echocardiography and perfusion SPECT give the same information on the presence, the site, the extent and the severity of myocardial ischemia in patients with single vessel disease of the left anterior descending artery. The results of post-exercise echocardiography are strongly dependent on the skill of the operator to record good quality images as soon as possible after termination of exercise. Furthermore, wall motion is the most difficult echocardiographic parameter to evaluate. In the present study, echocardiographic images were interpreted by two observers (because this is the policy in our center); however, the low inter- and intra-observer variability for stress echocardiography in our laboratory indicates that this is not relevant for clinical test utilization, provided a good and long specific training be done. On the other hand, perfusion scintigraphy requires high cost equipment not always readily available. The choice of the 'best' method relies on the facilities available in the institution and on the level of expertise of the individual laboratory.

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CHAPTER 6.

Exercise echocardiography versus thallium-201 SPECT for assessing patients before and after PTCA.

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Exercise echocardiography versus thallium-201 SPECT for assessing patients before and after PTCA

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KEY WORDS: Stress echocardiography, SPECT, PTCA.

This study was designed (1) to assess the relationship between stress exercise echocardiography (echo) and 201-Tl single photon emission computed tomography (SPECT) applied simultaneously in 23 patients who were candidates to percutaneous transluminal coronary angioplasty (PTCA), (2) to assess the relationship between the development of exercise-induced wall motion abnormalities, transient perfusion defects and the severity of quantitatively assessed coronary stenoses and (3) to compare the functional improvement after PTCA by exercise echo and SPECT. Before PTCA there was an agreement of 78% between stress echo (new wall motion abnormalities) and SPECT (transient perfusion defects) results. All patients with a percentage diameter stenosis >70% had a positive echo and SPECT, while they were both negative if the percentage diameter stenosis was <50%. In 19 patients re-studied 4 weeks after PTCA, an ischaemic response at stress echo was found in two of the 13 patients who had a positive stress echo test before PTCA, and SPECT was still positive in three of the 10 patients who had a positive SPECT study before PTCA. Echo and SPECT were concordant in 17/19 cases. It is concluded that exercise echo and 201-Tl SPECT are useful non-invasive tools for the functional assessment of patients before and after PTCA, and that they provide highly concordant results.

Introduction

Non-invasive assessment of patients with coronary artery disease is of paramount importance for clinical decision making and prognostication. There is an increasing consensus that digital stress echocardiography provides such a useful diagnostic tool[1–6], while 201-Tl single photon emission computed tomography (SPECT) became state of the art procedure for studying myocardial perfusion[7–9]. Since both techniques provide useful information it is important to assess their relative advantages.

The aim of this study was (1) to assess the relationship between exercise echo and 201-Tl SPECT for the diagnosis of myocardial ischaemia in a group of patients before PTCA, (2) to clarify the relationship between the development of exercise-induced wall motion abnormalities assessed by echo, transient myocardial perfusion defects on SPECT and the severity of quantitatively assessed coronary stenoses, and (3) to compare results after successful PTCA with both stress echo findings and SPECT.

Patients and methods

STUDY PATIENTS

The study group included 26 patients with stable angina pectoris prospectively enrolled and who were candidates for PTCA. Of these, 23 had a good quality simultaneous stress echo and 201-Tl SPECT study. Twenty-one of these underwent PTCA which was technically successful in 19. These were re-studied with stress echo and 201-Tl SPECT 4 weeks after the procedure. Of the four patients who did not undergo a sequential study, two did not undergo PTCA because of remission of symptoms and two had a non-successful PTCA. The individual patient characteristics and the results of bicycle ergometry, stress echo and SPECT are represented in Table 1. Beta blockers were withdrawn 2 days before the test, while other medication was continued. Stress echocardiography and 201-Tl SPECT were not used for selecting these patients for PTCA, since the indication had already been given based on clinical evaluation and coronary arteriography.

EXERCISE TESTING PROCEDURE

Symptom-limited upright bicycle ergometry was performed with stepwise increments of 20 Watts each minute. The ECG was continuously monitored (leads II, V_2 and V_5). A 12-lead ECG recording was obtained at rest and each minute during the exercise and cuff blood pressure measurement every 2 min. Computer averaging of the electrocardiographic complexes was performed by the Schiller system Cardiovit CSG/12. An ischaemic response was defined as ≥1 mm horizontal or downsloping ST segment depression occurring at 80 ms after the J point.

SPECT THALLIUM-201 SCINTIGRAPHY

One minute before the exercise was terminated, 111 MBq of thallium were injected intravenously. The patients were imaged with a rotating gamma camera

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(Siemens Gammasonics Rota-camera, Orbiter) 5 min and 4 h after thallium injection. Thirty-two projections were obtained (from left posterior oblique to right anterior oblique projection) with an acquisition time of 45 s per projection. The digitizing matrix (64 × 64 word mode) was selected in the mid portion of the camera image by using a zoom factor of $\sqrt{2}$. The tomographic data were processed on a Gamma 11 computer system with a floating point processor. Transaxial tomograms were reconstructed with the commercially available SPETS package (Nuclear Diagnostics AB, Hagsten, Sweden). From the three-dimensional data cube, slices were selected both perpendicular and parallel to the long axis. For each patient, six oblique (short axis) slices were defined from the apex to the base and three sagittal slices from septum to the lateral wall. To compare exercise and reperfusion studies, the short axis and the sagittal slices were displayed as pairs and interpreted by two experienced observers without knowledge of clinical and echocardiographic results. The slices were four pixels thick, partially overlapping. Each short axis slice was divided into eight approximately equal-sized regions; the septal part of the upper two slices (four segments) was not evaluated, since this portion corresponds to the fibrous interventricular septum and thus may show reduced thallium uptake. The apical region was evaluated from the three central sagittal cross sections, yielding a total of 44 + 3 = 47 segments per patient study. The thallium uptake of each segment was graded semiquantitatively, based on a five-point scoring method (0 = normal, 1 = slightly reduced, 2 = moderately reduced, 3 = severely reduced, 4 = absent uptake). Ischaemia was defined based on the presence of a stress perfusion defect that partially or completely resolved at the delayed imaging. Because of its doubtful meaning, a post-exercise score of 1 with normal score at redistribution imaging was not considered as ischaemic. Perfusion scores were then calculated by summing the scores of all the segments, both in the post-exercise and in the rest studies.

EXERCISE ECHOCARDIOGRAPHY

Two-dimensional echocardiograms were performed in the left lateral decubitus position before and immediately after exercise, using a commercially available wide angle phased array imaging system (Hewlett Packard Sonos 1000). Examination at rest included conventional parasternal long- and short-axis views and apical four- and two-chamber views. Transducer positions were marked on the patient's chest wall; if coincident with those of one of the ECG precordial leads, the electrode was placed in a lower intercostal space. Immediately after exercise, the patient reassumed the same left lateral decubitus and the post-exercise study was obtained from the same echocardiographic windows. As a result, thallium scanning was not delayed, and imaging always began within 5 min of the end of the exercise. Both rest and stress studies were recorded on videotape and digitized on-line with a Nova Microsonics PreVue III System (ATL). This system allows the user to display pre- and post-exercise images of each standard echocardiographic view side by side in two different quad-screen formats. Final echocardiographic

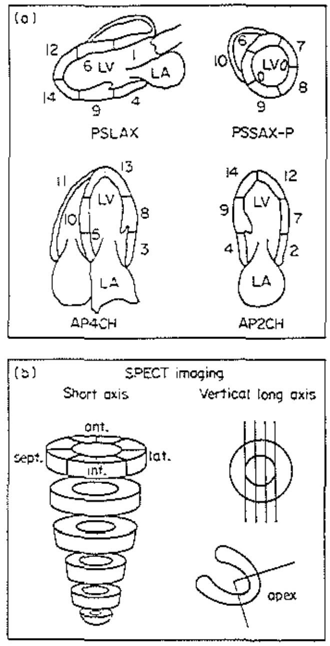

Figure 1 Schematic representation of the segmentation used for assessing echocardiography (1a) and SPECT (1b).

data were stored on a 5·25 inch double-side high-density floppy disk for later analysis. All echocardiograms were analysed by two experienced observers unaware of the results of the ergometric test, scintigraphic data or coronary angiography. For purposes of analysis, the left ventricular wall was divided into 14 segments (Fig. 1a). In each study, wall motion was visually evaluated at rest and after exercise and graded as 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic.

A wall motion score index was defined by the sum of the scores of all the segments divided by the number of segments. The difference in wall motion score indices between the post-exercise and rest studies was then calculated; thus, a difference of 0 represented a normal examination. On the other hand, the difference in the scores between post- and pre-PTCA studies gave information on the results of the procedure.

The inter and intra-observer reproducibility of the interpretation of the SPECT imaging and stress echo in our institution is good, as previously reported[10,11], both for the scoring system[10] and for the diagnosis of an ischaemic response where the agreement ranged from 85 to 92%[11].

CORONARY ANGIOGRAPHY

Coronary cineangiograms were analysed semiquantitatively with a PC-based coronary analysis system with a manual caliper program in its basic configuration developed in our centre[12]. For this purpose, the cinefilm is

Table 1 Baseline characteristics and results after PTCA in all individual patients

Patient		1	2	3	4	5	6	7	8	9	10	11	12	13
Age (years), sex (M/F)		m 62	m 64	m 56	f 56	m 62	m 50	f 62	f 64	m 57	m 73	m 65	m 55	m 62
Previous MI		−	+ non-q	−	−	+ non-q	−	−	−	+ non-q	+	−	−	+
Exercise ECG														
Watt	B	80	140	120	140	140	120	120	120	140	140	140	120	120
	A	140	140	/	120	150	100	100	100	130	140	133	/	/
	N	163	164	166	130	148	182	92	110	156	109	133	156	156
Max HR	B	118	105	125	163	143	130	154	144	112	135	125	149	134
	A	123	149	/	164	102	150	162	148	160	139	135	/	/
Angina/	B	+/+	+/+	−/+	− −	+ +	+ −	+/−	+/−	+/−	−/−	+/+	+/+	− −
ST-depression	A	−/+	+/+	/	− −	− +	−	−/−	−/−	−/−	−/−	−/−	/	/
Vessel(s) disease		LAD	LCX	RCA LCX	RCA	LCX	LCX	RCA	LAD	RCA	RCA	RCA	LCX	RCA
Stenosis diameter (%)		77	64	100 60	70	62	58	74	39	59	58	75	100	80
Residual diameter stenosis after PTCA (%)		27	0	/	14	100	21	35	21	3	23	29	/	/
Echo														
Ischaemia	B	+	+	/	−	+	+	+	−	+	+	+	+	/
	A	−	−	/	−	+	−	+	−	−	−	−	/	/
Exercise WM score	B	1·86	1·50	/	1·28	1·28	1·64	1·42	1	1·21	1·07	1·78	1·50	/
	A	1	1·07	/	1·28	1·1	1·42	1·42	1	1	1	1·07	/	/
Resting WM score	B	1·07	1	/	1·28	1	1·50	1	1	1	1	1·07	1	/
	A	1	1·07	/	1·28	1	1·42	1·14	1	1	1	1·07	/	/
SPECT														
Ischaemia	B	+	+	+	−	+	−	+	−	+	−	+	/	−
	A	−	−	/	−	+	−	+	−	−	−	−	/	/
Exercise score	B	30	28	26	1	27	87	33	3	13	18	40	/	40
	A	1	18	/	1	16	82	10	1	2	15	6	/	/
Resting score	B	4	18	15	5	11	82	8	1	6	21	2	/	45
	A	2	18	/	5	0	80	4	12	5	11	7	/	/

B: before PTCA; A: after PTCA; N: normal expected values; WM: wall motion.

mounted on a standard Tagarno 35 CX projector with built-in video camera. A selected cineframe is then converted into video format, digitized at a resolution of 512 × 512 × 8 bits and displayed on a video monitor. For calibration purposes, a region-of-interest (ROI) around the contrast catheter is selected with the mouse of the system, magnified two-fold with linear interpolation and displayed on the video monitor for subsequent measurements. Next, the user indicates with the mouse three pairs of points at either side of the magnified catheter segment. The average value of the measured width expressed in pixels is then compared with its true size (in mm), resulting in a calibration factor in mm pixel^{-1}. Following this the arterial segment to be analysed is magnified two-fold and linearly interpolated, and the user similarly defines the obstruction and reference diameters. From these absolute values, percentage diameter stenosis can be calculated simply.

STATISTICAL ANALYSIS

Analysis of the data was performed by paired and unpaired Student's t-test, when appropriate.

Results

The individual results are reported in Table I.

ASSESSMENT BEFORE PTCA

Relation between ergometric results, stress echo and SPECT

Before PTCA the median working capacity was 140 Watts (range 80–200), and the median maximal heart rate was 134 beats min^{-1} (range 100–167). In Table 2 the results of echo and SPECT have been summarized separately according to the symptomatic and the electrocardiographic responses to bicycle ergometry. The results indicate a similar prevalence of positive echo and SPECT in the groups with a different response to exercise electrocardiography.

Concordance of an ischaemic response by stress echo and SPECT

An ischaemic response during exercise was found by echo in 14/23 cases and in 11/23 cases by SPECT. As shown in Fig. 2 there was an agreement of 78%. In the four cases where echo was positive and SPECT did not show transient perfusion defects, a 'fixed' perfusion defect was present, consistent with the diagnosis of a previous myocardial infarction. In all cases with an ischaemic response, both by echo and SPECT, the location of the abnormality was consistent with the distribution territory of the stenotic vessel.

Patient		14	15	16	17	18	19	20	21	22	23	24	25	26
Age (years), sex (M/F)		m	m	f	m	m	m	m	m	m	f	m	f	m
		50	56	65	51	63	51	60	43	54	63	62	61	43
Previous MI		+	−	−	−	+	+	−	−	−	−	+	−	−
		non-q			non-q		non-q							
Exercise ECG														
Watt	B	200	100	120	160	140	180	160	180	140	120	140	90	160
	A	200	/	125		200		150	200	160	120	160	/	170
	N	176	166	107	181	220	159	158	190	158	117	150	120	208
Max HR	B	152	118	134	156	153	159	101	134	134	167	122	100	120
	A	141	/	143		177		125	151	133	170	140	/	130
Angina/	B	+ +	+/+	+/+	− −	+ +	− +	−/+	− +	− +	+/+	−/−	+/−	+/−
ST-depression	A	− −	/	−/−		− −		−/−	− −	− −	−/−	−/−	/	−/−
Vessel(s) disease		LAD	LAD RCA	LCX	LCX	LAD	LAD	RCA	LCX	LAD	LAD	RCA	RCA LAD	LAD
Stenosis diameter (%)		57	100 68	59	> 50 (visual)	60	43	73	69	74	52	67	57 66	58
Residual diameter stenosis after PTCA (%)		34	/	14		39		13	21	35	30	5	/	20
ECHO														
Ischaemia	B	+	+	−	−	+	−	+	−	+	−	+	−	−
	A	−	/	−		−		−	−	−	−	−	/	−
Exercise WM score	B	1·42	1·64	1	1	1·42	1	1·64	1·14	1·71	1	1·28	1	1
	A	1	/	1		1		1·07	1·14	1·07	1	1·14	/	1
Resting WM score	B	1	1·14	1	1	1	1	1·07	1·14	1	1	1.14	1	1
	A	1	/	1		1		1·07	1·14	1·07	1	1·14	/	1
SPECT														
Ischaemia	B	−	+	+	−	+	−	+	−	+	−	−	−	−
	A	−	/	+		−		−	−	−	−	+	/	−
Exercise score	B	28	43	24	1	34	5	55	0	52	4	20	0	2
	A	1	/	11		10		12	0	13	3	19	/	2
Resting score	B	27	8	11	0	12		43	0	10	0	25	0	4
	A	19	/	4		4		15	0	13	1	18	/	3

Table 2 Relation between stress electrocardiography, echo and SPECT in 23 candidates for PTCA

Angina:	+	−	+	−
ST depression:	+	+	−	−
Number	11	3	5	4
Echo positive	8	2	2	2
SPECT positive	8	2	1	0

Echo positive: new wall motion abnormalities: SPECT positive: transient perfusion defects.

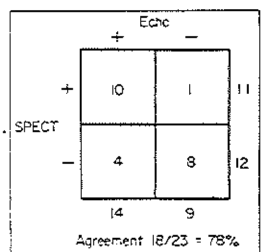

Figure 2 Two-by-two table indicating the relation between stress-induced new wall motion abnormalities (echo+) and transient perfusion defects (SPECT+) in 23 candidates for PTCA.

Relation between stress echo and SPECT results, and the severity of the coronary stenoses before PTCA

An ischaemic response was found in only some of the patients, 14/23 by echo and 11/23 by SPECT. In these patients a quantitative analysis of the coronary stenosis was technically possible in all but one patient. In Fig. 3 the severity of the coronary stenosis is compared in the groups of patients with a normal and an ischaemic response during exercise, by echo and SPECT. It clearly appears that the group of patients with an ischaemic response with either test had a more severe coronary stenosis as compared to those with a non-ischaemic response.

However, while patients with a diameter stenosis greater than 70% always had an ischaemic response, the group with a stenosis diameter between 50 and 70% had an unpredictable response to stress, independent of the vessel involved. The two patients with the least severe stenosis, less than 50%, both had a negative echo and SPECT. These two patients had been referred for PTCA based on symptoms, the results of bicycle ergometry and visual assessment of coronary angiogram (scored as more than 50% diameter stenosis).

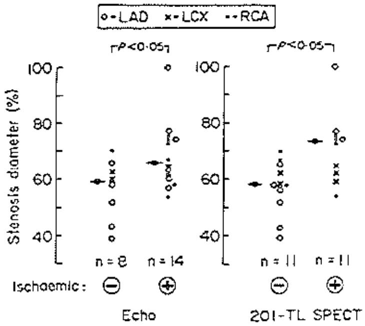

Figure 3 Comparison of percentage of diameter coronary stenoses in patients with a positive vs. negative echo and SPECT, before PTCA.

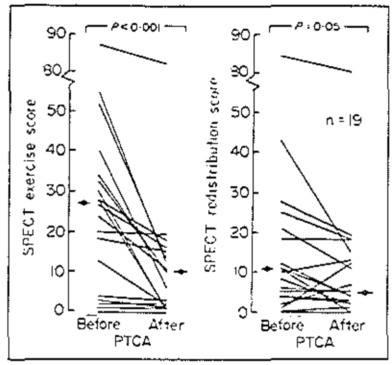

Figure 5 Changes of exercise and redistribution 201-Tl SPECT severity score before and after PTCA in 19 patients.

Table 3 Results of sequential bicycle ergometry, stress echo and SPECT in 19 patients before and four weeks after PTCA

	Before PTCA	After PTCA
Working capacity (Watts)	138 (SD 25)	144 (SD 31)*
Max heart rate (beats min⁻¹)	134 (SD 18)	143 (SD 18)*
Angina, n	11	2
ST segment depression, n	12	4
Echo positive, n	13	2
SPECT positive, n	10	4

*$P<0·05$.

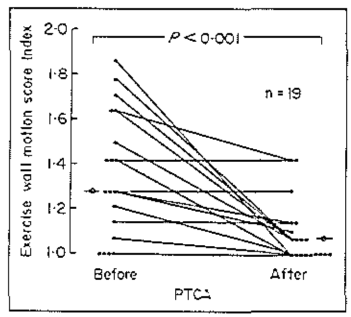

Figure 6 Immediate post-exercise echo severity score in 19 patients before and 4 weeks after PTCA.

		Echo +	Echo −	
SPECT	+	2	2	4
	−	0	15	15
		2	17	

Agreement 17/19 = 89%

Figure 4 Two-by-two table indicating the relation between stress-induced new wall motion abnormalities (echo+) and transient perfusion defects (SPECT+) in 19 patients, 4 weeks after PTCA.

FUNCTIONAL RESULTS AFTER PTCA

Sequential stress echo and SPECT were applied before PTCA and 4 weeks after PTCA in 19 patients. The overall results of ergometry, stress echo and SPECT are represented in Table 3. The results indicate that in this group of patients there was a dramatic decrease of stress-induced ischaemic responses after PTCA, as judged by angina, ST segment depression, stress echo and 201-Tl SPECT. Fig. 4 represents the agreement between stress echo and 201-Tl SPECT in the assessment of myocardial ischaemia after PTCA in these patients; it was very good (89%). In Figs 5 and 6 the individual changes after PTCA of the severity score by SPECT and echo are shown, which all significantly improved in this group. Of the SPECT score, it should be pointed out that not only the exercise but also the redistribution score improved by a similar extent, showing a decrement after PTCA of 61% and 58%, respectively.

Discussion

The main findings of this study are that in a cohort of PTCA patients, stress echocardiography and 201-Tl SPECT are both useful in assessing the functional significance of coronary lesions and that both techniques provide highly concordant information. Secondly, sequential stress echo and 201-Tl SPECT before and after PTCA are equally useful for detecting the directional changes of stress-induced new wall motion abnormalities or transient perfusion defects, which express different functional variations after revascularization. These results are not new, since separate echocardiographic and scintigraphic studies had already demonstrated similar findings[3–6]. However, this study is the first one in which both tests were applied simultaneously in the same patients. One earlier study had compared planar 201-Tl scintigraphy with exercise echo[1]; however, it is increasingly accepted that SPECT is superior to planar scintigraphy[7]. Furthermore, SPECT is more suitable for comparison with echocardiography, both techniques being tomographic.

Our findings, as represented in Fig. 2, indicate that before PTCA there was on average a good agreement (78%) for 'ischaemic' responses between the two techniques; however, four patients had a positive echo with a SPECT result which was classified as non-ischaemic. Although the number of patients is low, it is worthwhile to note that three of these patients had a previous myocardial infarction, which was consistently imaged by SPECT as a fixed perfusion defect. It has recently been observed in different studies that a fixed 201-Tl perfusion defect can also be consistent with myocardial ischaemia, since (1) in some of these patients a partial redistribution is apparent only if a later scan is performed 12–24 h after exercise[13], and (2) since part of such fixed defects may be reversible after revascularization[10]. Therefore, the 'false' negative SPECT studies could be partially explained by the fact that in our study redistribution scan was obtained only at 4 h after exercise. These findings are important since they underscore and confirm a pitfall of usual protocols with 201-Tl scintigraphy therefore suggesting that later imaging or a re-injection of 201-Thallium is indicated in patients with a persistent defect on the usual 4-h images.

It will also be interesting to assess in future studies whether, as suggested by our initial experience in a different study[14], the number of 'false negatives' by nuclear perfusion studies will be reduced with the newer Tc 99m labelled radiotracers (MIBI)[15], which are characterized by an absence of redistribution, in contrast to 201-Tl.

In contrast with most studies, we utilized a quantitative method for assessing the severity of coronary lesions[12] to which the non-invasive tests were compared. This would allow assessment of the cut-off value beyond which a coronary stenosis becomes functionally important[16]. This point has been very recently stressed in an echocardiographic study by Sheikh *et al.*[5] who found a relation between the quantitatively assessed coronary stenosis and the results of exercise echo, which is very comparable to our findings. The importance of a quantitative assessment of coronary stenosis is illustrated in Fig. 3. It should be noted, however, that all the coronary lesions were scored as 50% or more by visual assessment. However, the diagram in Fig. 3 indicates that in two cases the stenosis was less than 50%, being 39% and 43%, but in both cases stress echo and SPECT were negative, consistent with a non-severe lesion.

Our results indicate that in all cases with a stenosis of more than 70%, both echo and SPECT were positive. In the intermediate zone (50 to 70% diameter stenosis), the response to exercise in these patients was unpredictable, with only about one-half being ischaemic on echo and/or SPECT. It is very important to underline that stress echo and 201-Tl SPECT provided very similar results when related to the severity of the coronary stenoses. Furthermore, three recent stress echocardiographic studies[4–6] and one study by 201-Tl SPECT[3] have shown that both techniques are useful for demonstrating improvements of regional wall motion, global left ventricular function and myocardial perfusion during exercise, after a successful PTCA. Our results in the 19 patients who underwent a second combined stress study 4 weeks after PTCA confirm these previous findings (Fig. 6). In addition, our study demonstrated that in this setting there is also an excellent agreement on the functional assessment of the individual patients (Fig. 4). In our experience, most patients already had a negative echo and SPECT results 4 weeks after PTCA. This is partially in disagreement with a recent scintigraphic study in which a resolution of the perfusion defect was only found some time after PTCA[4].

An additional interesting finding of our study on SPECT imaging was that after PTCA there was a parallel improvement of both initial exercise perfusion defects and of late redistribution defects (Fig. 5). This confirms previous findings[10] and indicates that a fixed or a partially reversible 201-Tl perfusion defect does not exclude the presence of viable and reversibly ischaemic myocardium.

LIMITATIONS OF THE STUDY

Although the results of the present study are consistent with those of others, this study includes only a small group of patients, and more should be studied in the future to validate these findings. SPECT imaging has been only semiquantitatively assessed; since it has been shown that a quantitative computer analysis provides a more accurate information, this type of analysis should be applied to explore whether a better separation could be achieved in patients with a different severity of coronary stenosis. Finally, coronary angiography was not repeated 4 weeks after PTCA to ascertain the consistency of the non-invasive evaluation of re-stenoses.

In conclusion, our study indicates that exercise echocardiography and 201-Tl SPECT are both useful tools for assessing the functional severity of coronary stenosis and the functional results after PTCA. Since the two techniques are both superior to stress electrocardiography alone and provide similar information, and if these results are confirmed, stress echocardiography could become the technique of choice in this clinical setting. It is clear that stress echocardiography offers some definite advantages compared to nuclear studies mainly due to the lower costs and the lack of radiation. However, due to the considerable skill and commitment required by stress echocardiography, the final choice of one or the other method will depend on the relative strength and reliability of the local laboratories of nuclear medicine and stress echocardiography.

We wish to thank all the technicians of the nuclear medicine laboratory, for their useful cooperation in the acquisition of the combined nuclear and echocardiographic studies.

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CHAPTER 7.

Comparison of exercise echocardiography with myocardial perfusion scintigraphy for the diagnosis of coronary artery disease.

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Comparison of exercise echocardiography with myocardial perfusion scintigraphy for the diagnosis of coronary artery disease

Summary

The rationale of exercise echocardiography for the diagnosis of coronary artery disease is based on the detection of exercise-induced wall motion abnormalities by ultrasound. Some of the problems that had previously limited the widespread application of the test have been solved by the development of digital recording and side by side cine loop display of two-dimensional echocardiograms: thus, respiratory artifacts can be eliminated, the examination is faster, and the comparison between rest and stress images has become practical and reliable improving sensitivity.
The sensitivity and specificity of exercise echocardiography vary from 70 to 100%, according to patient selection, the protocol, and the gold standard used. Few studies studied the value of exercise echocardiography as compared to the more established nuclear cardiology imaging. Data from these comparative evaluations show a strong correlation between the two techniques for identifying and localizing myocardial ischemia.
With good equipment and after proper training, exercise echocardiography can provide both diagnostic and prognostic information for routine clinical care.

Zusammenfassung: Vergleich von Belastungsechokardiographie mit myokardialer Perfusionsszintigraphie hinsichtlich der Diagnostik einer koronaren Herzerkrankung

Die Entwicklung der digitalen „Cine-Loop"-Technik hat zur Lösung des Problems beigetragen, mittels Belastungsechokardiographie auswertbare Bilder bei maximaler Belastung oder unmittelbar danach zu erhalten, und zum wachsenden Interesse an dieser Methode geführt. Vorliegend stellen wir unsere Erfahrung mit der Belastungsechokardiographie, insbesondere auch den Vergleich zur Myokardszintigraphie dar.

Zweidimensionale Evaluierung von Wandbewegungsstörungen (Tabelle 1)

Im Unterschied zu Belastungs-EKG und Szintigraphie wird mittels Belastungsechokardiographie die Ischämie durch ihre mechanische Auswirkung, die Entwicklung einer regionalen Asynergie, die als einziges Kriterium für einen positiven Befund gilt und sensitiver sowie spezifischer ist als konventionelle EKG-Veränderungen und Schmerz, erfaßt. Szintigraphisch dient lediglich eine Maldistribution des Radionuklids als Ischämiemarker.
Weitere Vorteile der Belastungsechokardiographie (Tabelle 1) sind: die direkte Beurteilbarkeit der Wandbewegung, ihre Sicherheit und Wiederholbarkeit und damit Möglichkeit zur serienmäßigen Untersuchung, die einfache Technik, die relativ geringen Kosten, die hohe Spezifität, da die Entwicklung neuer oder ausgeprägterer Wandbewegungsstörungen Ischämie voraussetzt, die unmittelbare Evaluierung der Resultate selbst bei digitaler Akquisition, die kurze Untersuchungszeit, die Möglichkeit, aufgrund der tomographischen Technik nahezu jedes Segment des linken Ventrikels zu beurteilen, die Möglichkeit der gleichzeitigen Evaluierung von linksventrikulärer Funktion und Ischämie.
Nachteile sind die Abhängigkeit der Untersuchungstechnik vom Untersucher sowohl hinsichtlich Datenaufnahme als auch Auswertung, die Bildqualität, die jedoch infolge einer Weiterentwicklung der Geräte und computerisierten Bildverarbeitung verbessert wurde mit Erfolgsquoten von mittlerweile 90%, im eigenen Krankengut von 97% gegenüber 75 bis 80%, sowie die fehlende Information über die metabolische Aktivität des Herzens.
Ein Vergleich verschiedener Studien hinsichtlich der Diagnostik einer koronaren Herzerkrankung mittels Belastungsechokardiographie und Koronarangiographie (Tabelle 2) ist durch unterschiedlich gewählte Belastungsarten wie Fahrradergometer oder Laufband und unterschiedlich gewählte Akquisitionszeitpunkte wie während maximaler oder unmittelbar nach Belastung erschwert. Belastungsinduzierte Wandbewegungsstörungen dauern zwar in der Regel ein bis fünf Minuten nach Beendigung der Belastung noch an, bei weniger ausgeprägter Ischämie kommt es jedoch zu einer rascheren Erholung. So konnte mit Bildern, die unter maximaler Belastung aufgenommen wurden, im Vergleich zu Aufnahmen, die nach Belastung registriert wurden, eine geringe Verbesserung der Sensitivität erzielt werden.

Vergleich der mittels Belastungsechokardiographie und Perfusionsszintigraphie erhaltenen Resultate

Bei Patienten ohne Myokardinfarkt wurde in einer Studie eine Sensitivität zur Erkennung einer signifikanten koronaren Herzerkrankung von 83% mittels Belastungsechokardiographie und von 74% mittels planarer Thalliumszintigraphie bei einer jeweiligen Spezifität von 92% ermittelt. Bei Mehr-Gefäß-Erkrankung lag die Sensitivität mit 94% höher als bei Ein-Gefäß-Erkrankung mit 50%. Wird das Thalliumszintigramm als Referenzmethode herangezogen, konnte mittels Belastungsechokardiogramm mit einer Sensitivität von 100% und einer Spezifität von 93% eine koronare Herzerkrankung diagnostiziert werden. Mit der Einführung der „Single-Photon"-Emissionscomputertomographie (SPECT) wurde die diagnostische Treffsicherheit der Thalliumszintigraphie erhöht.

In eigenen Untersuchungen wurden echokardiographische Bilder in Ruhe und unmittelbar nach Belastung am Fahrradergometer in aufrechter Position mittels eines digitalen „Cine-Loop"-Systems aufgezeichnet und Ruhe- und Belastungsaufnahmen zum besseren Vergleich nebeneinander abgespielt. Bei 103 Patienten mit nachgewiesener oder vermuteter koronarer Herzerkrankung fand sich eine gute Korrelation zwischen der mittels MIBI-(Methoxyisobutylisonitril-) SPECT erhobenen regionalen Myokardperfusion und echokardiographisch erhobener Wandbewegung in Ruhe und unmittelbar nach Belastung, wobei die Untersuchungen jeweils simultan durchgeführt wurden. Mittels MIBI-SPECT ergab sich häufiger ein positiver Befund als mittels Echokardiographie. Von den Patienten mit diskrepantem Befund wiesen 90% reversible Perfusionsdefekte im Bereich der inferioren bzw. der posterolateralen Wand auf; auch fand sich bei Patienten mit vorausgegangenem Myokardinfarkt häufiger ein positiver SPECT-Befund.

Die diskrepanten Befunde lassen sich in verschiedener Weise erklären:

– rasche Erholung von belastungsinduzierten Wandbewegungsstörungen geringen Ausmaßes,
– Wandbewegungsstörungen in Regionen, die mittels zweidimensionaler Echokardiographie schwierig erfaßbar sind (fehlender Kurzachsenschnitt in Höhe der mittleren Papillarmuskeln),
– Wandbewegungsstörungen in Ruhe bei Zustand nach Myokardinfarkt, die die Erkennung von belastungsinduzierten Wandbewegungsstörungen erschweren,
– Maldistribution des koronaren Blutflusses statt wirklicher Ischämie.

Auch bei Patienten mit angiographisch gesicherter Ein-Gefäß-Erkrankung fand sich eine gute Übereinstimmung echokardiographischer und perfusionsszintigraphischer Befunde mit 79%. Der Schweregrad der koronaren Herzerkrankung stand in Relation zur Entwicklung eines positiven Testergebnisses; so lag die Häufigkeit eines positiven Resultates bei >70%igen Stenosen bei 91%, bei 50- bis 75%igen Stenosen lag sie bei 50% und bei <50%igen Stenosen bei 14%. Mittels SPECT fand sich bei mittlerem Schweregrad von 50 bis 75% eine Sensitivität von 61%. Inter- und Intraobservervariabilität waren unserer Erfahrung nach bei der Belastungsechokardiographie minimal. Die Anwendung von Algorithmen zur routinemäßigen quantitativen Analyse von Wandbewegungsstörungen wird durch die Bewegung des Herzens im Raum und die suboptimale Auflösung bei den meisten klinischen Untersuchungen verhindert, so daß die subjektive Interpretation die praktikabelste Beurteilungsform bleibt. Umgekehrt bietet die quantitative SPECT verläßliche Information hinsichtlich Größe des Perfusionsausfalles und dessen Lage.

Vergleich der mittels Belastungs-EKG und Belastungsechokardiographie erhobenen Resultate

ST-Strecken-Veränderungen weisen einen Mangel an Sensitivität und Spezifität bei der Diagnostik einer koronaren Herzerkrankung auf und geben keine Information hinsichtlich Lage und Ausmaß einer Ischämie. Im Vergleich dazu scheint die Belastungsechokardiographie eine höhere Sensitivität insbesondere bei Mehr-Gefäß-Erkrankung aufzuweisen bei vergleichbarer Spezifität (Tabelle 2). So lag die Sensitivität bei 49 Patienten des eigenen Krankengutes mit koronarer Herzerkrankung für ST-Strecken-Senkungen bei 55% und für die Befunde der Belastungsechokardiographie bei 71%.

Indikationen für die Belastungsechokardiographie

1. Ein nicht diagnostischer Belastungs-EKG-Befund, der bei etwa 30% der Patienten vorkommt, insbesondere bei asymptomatischer ST-Strecken-Senkung, Brustschmerz ohne EKG-Veränderungen, abnormem Ruhe-EKG bei Linksschenkelblock, linksventrikulärer Hypertrophie mit Repolarisationsstörungen, WPW-Syndrom, unter Digitalistherapie oder nach Myokardinfarkt. 77% der Patienten mit einem nicht diagnostischen Belastungs-EKG-Befund wiesen im eigenen Krankengut übereinstimmende Befunde von Belastungsechokardiographie und Myokardszintigraphie auf, 30% der Patienten übereinstimmend positive Ergebnisse.
2. Evaluierung der Resultate einer Koronarangioplastie; die Belastungsechokardiographie kann zur Identifikation von Patienten, die von einer wiederholten Angiographie profitieren werden, sowie zu Verlaufsuntersuchungen dienen.
3. Bei Patienten nach Myokardinfarkt gleichzeitige Bestimmung von linksventrikulärer Funktion und Restischämie; die Lage der belastungsinduzierten Wandbewegungsstörungen gibt Hinweise auf das Ausmaß der koronaren Herzerkrankung. Ein positives Resultat gilt als Prädiktor für nachfolgende kardiale Ereignisse.
4. Evaluierung der funktionellen Bedeutung angiographisch subkritischer Stenosen. Sie kann damit wesentlich zur klinischen Entscheidungsfindung beitragen.

Myocardial perfusion scintigraphy has been widely used for the noninvasive diagnosis of coronary artery disease [6, 14, 18]. In the past years, exercise echocardiography has been proposed as a practical and useful diagnostic tool for the evaluation of patients with suspected or proven coronary artery disease, but the difficulty of acquiring good images at peak or immediately after stress had limited its use [5, 11, 15–17, 28, 29]. Recently, the development of digital cine loop acquisition systems has overcome this problem, leading to increased interest in this method [2, 7, 24]. In this article we review our experience with exercise echocardiography, with special reference to its comparative usefulness with myocardial perfusion scintigraphy.

Two-dimensional echocardiographic examination for wall motion abnormalities: advantages and disadvantages

Based on the evaluation of the ischemia-induced wall motion abnormalities, exercise echocardiography offers some theoretical and practical advantages over other noninvasive methods for detecting coronary artery disease (Table 1): ventricular wall motion can be evaluated, the examination is safe and repeatable, it does not require sophisticated techniques, allows for serial evaluation of ventricular wall motion, and its cost is relatively low. The test is highly specific, since myocardial ischemia is requested for the development of new or worsened wall motion abnormalities; the results are immediately evaluated, even when digital acquisition is performed; the time to complete the examination is short and no much longer than the time requested for the exercise ECG testing alone; the tomographic technique allows the assessment of almost every segment of the left ventricle. From the physiopathological point of view, the main difference between exercise echocardiography, ECG testing and scintigraphy resides in the different markers of myocardial ischemia. With exercise echocardiography, ischemia can be detected through its mechanical marker, which is more sensitive and specific when compared to the conventional marker of ECG changes and pain. Moreover, the development of a regional asynergy is the only criterion of positivity, and therefore myocardial ischemia is required, unlike with perfusion scintigraphy, where the marker is a maldistribution of the radiotracer.

As with any technique, exercise echocardiography has disadvantages. A major disadvantage is that the technique is operator dependent, both for collection of data and for analysis of images. Wall motion is the most difficult parameter evaluated with echocardiography: thus, a long training is required to become an experienced operator and successful application of this technique [19]. In the past years, the image quality was a limitation, since success rates of obtaining good quality images were only of 75 to 80%. Due to the use of more sensitive equipment and the availability of computer-assisted image processing (which facilitate the acquisition of two-dimensionl echocardiograms), most laboratories now report success rates in excess of 90%. Finally, exercise echocardiography is dependent on development of the end effect of myocardial ischemia, i.e. wall motion abnormalities, but does not give information on the metabolic activity of the heart.

	Echo	SPECT
Ventricular wall motion	+++	+ (gated)
Serial studies	+++	+
Low cost	++	+
Specificity for ischemia	+++	++
Ischemia as end-point	+++	–
No radiation exposure	+++	–
Tomographic imaging	+++	+++
Operator unrelated	+	+++
Perfusion	+	+++
Quantification	+	+++
Easy interpretation	+	+++

Table 1. Exercise echocardiography versus perfusion SPECT imaging.

Tabelle 1. Vergleich zwischen Belastungsechokardiographie und Perfusions-„Single-Photon"-Emissionscomputertomographie (SPECT).

Problems with different exercise modalities

Several studies have compared the results of exercise echocardiography with those of coronary angiography (Table 2) [3, 5, 10, 15–17, 20, 23, 27–29]. A direct

Authors	Year	Echo Sens	Spec	ECG Sens	Spec
Wann et al. [29]	1979	67	100	29	100
Morganroth et al. [17]	1981	63	91	59	91
Maurer and Nanda [16]	1981	70	92	52	77
Quinones [23]	1984	92	88	–	–
Crawford et al. [5]	1983	72	100	–	–
Limacher et al. [15]	1983	91	88	71	94
Visser et al. [28]	1983	69	92	58	85
Ginzton et al. [10]	1984	70	100	48	100
Jaarsma et al. [12]	1986	77	95	–	–
Armstrong et al. [3]	1987	87	86	–	–
Sheikh et al. [27]	1990	81	92	23	92
Pozzoli et al. [20]	1991	71	96	55	81

Table 2. Results of exercise echocardiographic studies. (Echo = exercise echocardiography; ECG = exercise ECG test. Values for sensitivities [Sens] and specificities [Spec] are expressed as %.)

Tabelle 2. Ergebnisse verschiedener Studien zur Belastungsechokardiographie. (Echo = Belastungsechokardiographie; ECG = Belastungs-EKG; Werte für Sensitivität [Sens] und Spezifität [Spec] sind in Prozent ausgedrückt.)

comparison of these studies is not easy, due to the different modality of exercise (bicycle or treadmill) and the different timing of image acquisition (peak or immediate recovery period). Although previous studies have demonstrated that exercise-induced wall motion abnormalities persist for one to five minutes after termination of exercise [16, 29], some patients, especially if the ischemia is not severe, exhibit a rapid recovery of their wall motion changes after exercise. Presti et al. [22] compared the results of stress echocardiography at peak exercise and after bicycle exercise. They concluded that the addition of echocardiographic images at peak exercise slightly enhances the sensitivity for the detection of coronary artery disease with exercise echocardiography.

Comparison with myocardial perfusion scintigraphy

Exercise echocardiography has been compared to radionuclide exercise tests in few studies. Maurer and Nanda [16] have shown in patients without previous infarction a sensitivity for detecting "significant" coronary disease of 83% by exercise echocardiography and of 74% by exercise redistribution planar thallium scintigraphy. The specificity was 92% with both methods. Sensitivity was much higher in patients with multi-vessel disease than in patients with single-vessel disease (94% vs 50%). Heng et al. [11] reportet 100% sensitivity and 93% specificity for detecting coronary artery disease by exercise echocardiography, when thallium scans were used as gold standard. In both studies planar scintigraphy was performed. The introduction of single photon emission computed tomography, however, has significantly improved the diagnostic accuracy of the scintigraphic technique for detecting myocardial ischemia [6, 18].

We have evaluated the diagnostic accuracy of this technique at our institution using several standards, including myocardial perfusion scintigraphy (either with 201 Tl or 99m Tc MIBI) and coronary angiography. In recent years our laboratory was able to obtain analyzable two-dimensional echocardiograms in 97% of all patients studied. The combined echocardiographic and scintigraphic tests are performed simultaneously, in conjunction with the same upright bicycle exercise test. Two-dimensional echocardiograms are obtained at rest and immediately after a symptom-limited exercise test. The rest and post-exercise images are both digitized on-line, using a digital-cine-loop system; this system allows for subsequent review as a continuous loop format at various play-back speeds in a quad screen format. As a result, the pre- and post-exercise views are displayed in a side-by-side manner, making the comparison of the images easier. In a first study [21], we compared exercise echocardiography with MIBI (methoxyisobutylisonitril) SPECT in terms of their ability to elicit an ischemic response in 103 consecutive patients with either proven or suspected coronary artery disease. We found a good correlation between regional myocardial perfusion and regional wall motion, both at rest and after exercise. The data of this study also suggested that MIBI SPECT detects more patients and more ventricular regions with "ischemia". Among patients with "ischemia" on SPECT, but without new or worsened wall motion abnormalities, 90% had reversible perfusion defects in the inferior and/or posterolateral wall. Moreover, there was a trend towards this pattern of disagreement (SPECT positive, echo negative) for patients with a previous myocardial infarction, in which the SPECT imaging was more frequently positive.

These findings can be explained in several ways:
- the rapid recovery of small areas of exercise-induced wall motion abnormalities;
- the development of wall motion abnormalities in areas which are difficult to be picked up by two-dimensional echocardiography;
- the presence of significant wall motion abnormalities at rest in patients with previous myocardial infarction, which make it difficult to detect exercise-induced wall motion abnormalities;
- maldistribution of coronary blood flow, rather than true ischemia.

The relative importance of these factors was analyzed in more detail [20, 26] and our findings suggest that these patients have a smaller ischemic zone than patients with both tests positive. Furthermore, the inability to record short-axis views at mid-papillary muscle level and/or a delay in acquiring post-exercise imaging play a critical role in determining these "false-negative" echocardiographic studies. Indeed, the endocardial surface is more perpendicular to the echocardiographic beam in the parasternal views than in the apical views, and thus the ability to detect subtle wall motion abnormalities is related to the use of multiple views.

We also evaluated the relationship between exercise echocardiography and perfusion SPECT in a group of patients with single-vessel disease of different severity assessed by quantitative coronary arteriography [26]. Again, there was a good overall agreement between the echocardiographic and the perfusion imaging (79%). Compared to patients with both tests positive, patients with negative echocardiogram and positive SPECT required a longer time for acquiring post-exercise echocardiographic images, and the ischemic area was smaller (as reflected by a lower mean ischemic perfusion score index). Accordingly, the time needed for acquiring the stress echocardiographic images play a very important role in assessing the severity of disease with exercise echocardiography. Our results also showed that the severity of coronary artery disease is related to the development of a positive test; the incidence of a positive exercise echocardiography was 91% in patients with a diameter stenosis >70%, compared to 50% in patients with stenosis of intermediate severity (50 to 70%) and to 14% in patients with "non significant" coronary artery stenosis (< 50%).

It could be argued that visual assessment of wall motion is difficult, subject to bias and poorly reproducible; we have assessed inter- and intraobserver variability in a subgroup of patients, and we found them minimal [21]. This was due to the common and specific training in stress echocardiography that our group completed at the Thoraxcenter. We agree that a more objective method of evaluation would be desirable, but limitations of any quantitative method must be realized. The difficulty of correcting for spatial movements of the heart and the sub-optimal resolution of most clinical examinations hampers the application of algorithms for routine quantitative analysis. To date, subjective interpretation of wall motion abnormalities remains the most practical approach [13]. Conversely, our experience and that of others [4] indicates that quantitative SPECT offers reliable information, providing accurate determination of perfusion defect size and site.

Comparison with exercise ECG testing

Routine exercise ECG testing remains the most common test for the non-invasive assessment of coronary artery disease. However, ST segment abnormalities lack of sensitivity and specificity, and no information on the site and the extent of ischemia can be derived [9].

The comparison between exercise echocardiography and exercise ECG testing is represented in Table 2. In comparison with exercise ECG, exercise echocardiography appears to have better sensitivity (especially in identifying patients with multivessel disease) and comparable specificity. These data suggest that exercise echocardiography is a much better diagnostic test for coronary artery disease than exercise ECG testing, but there are practical and cost considerations limiting widespread routine application.

In our laboratory, analysis of the ECG recorded simultaneously with the exercise echocardiographic test showed that in a group of 49 patients with coronary artery disease, the exercise ECG was positive in 27 (55%) and normal in 22 (45%). In the same group of patients, sensitivity of exercise echocardiography was 71% [20].

Indication for exercise echocardiography

1. Patients with a non-diagnostic response to exercise test:

In our experience, a non-diagnostic exercise test occurs in approximately 30% of patients referred for evaluation. The non-diagnostic ECG response to exercise includes the following:
- Asymptomatic ST segment depression
- Chest pain without ECG changes
- Abnormal ECG at rest (left bundle branch block, left ventricular hypertrophy with left ventricular strain, Wolff-Parkinson-White syndrome, digitalis, post-infarction).

Our experience has shown that in this subset exercise echocardiography is of most value, offering the opportunity to identify patients with coronary artery disease. In the subgroup of patients with a non-diagnostic response to bicycle ergometry, 77% had concordant results between exercise echocardiography and myocardial perfusion scintigraphy and 30% had both tests positive [21]. Thus, exercise echocardiography could be the imaging procedure of choice for evaluating patients with non-diagnostic ECG response to exercise or in whom coronary artery disease is still suspected after a negative exercise testing.

2. Patients post-angioplasty:

Restenosis within six months occurs in about 30% of patients who undergo percutaneous transluminal coronary angioplasty. Exercise echocardiography will be of value in evaluating the results of coronary angioplasty, identifying those patients who would benefit from repeat angiography. Our experience indicates that exercise echocardiography is very helpful in the follow up of these patients, providing similar information to 201 Tl SPECT [8].

3. Patients who have had a myocardial infarction:

Exercise echocardiography offers the unique opportunity to evaluate both left ventricular function and residual ischemia in patients following myocardial infarction. The site of exercise-induced wall motion abnormalities allows to predict the extent of coronary artery disease. A positive exercise echocardiography is a strong predictor of subsequent cardiac events [25].

We found a slightly higher incidence of transient perfusion defects without new or worsened wall motion abnormalities in patients with a previous myocardial infarction when compared to patients without such a history [21], however, exercise-induced wall motion abnormalities in the infarct zone are difficult to detect because of significant wall motion abnormalities at rest [3].

4. Evaluation of the functional significance of coronary lesions which appear subcritical angiographically:

Exercise echocardiography is often helpful in evaluating some ambiguous coronary angiographic studies. We have already evaluated the correlation between exercise echocardiography, SPECT, and coronary angiography [26]; our findings indicate that for stenosis of intermediate severity (50 to 70%), new wall motion abnormalities were detected in 50% of the patients by exercise echocardiography and transient perfusion defects by SPECT in 61% of the patients. Although coronary angiography is used as the gold standard for coronary artery disease, the functional consequences of a given stenosis (as evaluated by exercise-induced wall motion abnormalities and/or transient perfusion defects) are often paramount in the clinical decision making.

Conclusion

Exercise echocardiography is a versatile and reliable technique with a diagnostic accuracy similar to that of the more established radionuclide tests. Digital cine loop acquisition and proper training are pre-requisites to utilize the potential role of this technique at its maximum. We totally agree that "exercise echocardiography is ready, willing and able for an expanded role in patient evaluation" [1].

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PART THREE

PHARMACOLOGICAL STRESS ECHOCARDIOGRAPHY

CHAPTER 8.

Dobutamine stress echocardiography: its role in the diagnosis of coronary artery disease.

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Dobutamine stress echocardiography: its role in the diagnosis of coronary artery disease

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KEY WORDS: Stress echocardiography, dobutamine, exercise testing.

We have assessed the usefulness of dobutamine infusion for the diagnosis of coronary artery disease by using two-dimensional echocardiography and 12-lead electrocardiogram. Dobutamine was infused at incremental doses (up to a maximum of 40 $\mu g\, kg^{-1}\, min^{-1}$) in 52 patients with chest pain: all the patients underwent coronary angiography; significant coronary artery disease was quantitatively defined as $\geq$50% diameter stenosis. Thirty-six patients were on betablockers. The test was considered positive when new regional wall motion abnormalities appeared during dobutamine infusion. No significant side effects occurred in any patient during the test. Transient wall motion abnormalities were detected in 20 of 37 patients with coronary artery disease (sensitivity=54%); ischaemic ST segment changes were present on ECG in nine patients (sensitivity=24%). Dobutamine stress echocardiography was negative in 12 of 15 patients with coronary artery diameter stenosis <50% (specificity=80%). Exercise electrocardiography (ECG) was performed in 35 of these 52 patients. Maximum heart rate and systolic blood pressure were significantly higher during exercise than during dobutamine stress test (127±23 vs 99±24 beats min^{-1}, $P<0{\cdot}0001$; 179±25 vs 152±30 mmHg, $P<0{\cdot}0001$). The exercise ECG test was positive in 12 of the 26 patients with significant coronary artery disease (sensitivity=46%), and dobutamine stress echocardiography in 16 (sensitivity=62%). Dobutamine stress echocardiography test is a safe and feasible diagnostic test for the noninvasive diagnosis of coronary artery disease and can be performed in patients unable to exercise. It provides similar diagnostic accuracy compared to routine exercise testing, adding information on the location and extent of myocardial ischaemia.

Introduction

The diagnosis of ischaemic heart disease relies on symptoms and on the typical ST segment changes on the ECG. However, myocardial ischaemia may occur in the absence of symptoms and electrocardiographic ST segment abnormalities lack both sensitivity and specificity[1]. Recently, exercise induced transient wall motion abnormalities detected by two-dimensional echocardiography have been used as additional markers of ischaemia[2,3], but obtaining good quality peak or post-exercise images is not always easy, even when a digital acquisition system is used. Therefore, alternative pharmacological stresses have been proposed, having the advantage of good quality two-dimensional echocardiograms and being applicable in patients unable to exercise. The most commonly used pharmacological stress is dipyridamole, a potent coronary vasodilating agent, and its use in both the diagnosis and prognosis of coronary artery disease is well established[4]. Less information is available on dobutamine, an adrenergic stimulator whose effect can be regarded as more similar to that of an exercise test[5].

The aim of the present study was to investigate the clinical value of dobutamine to provoke myocardial ischaemia detected by symptoms, ECG and two-dimensional echocardiography in a group of symptomatic patients who also underwent coronary angiography. Dobutamine test was also compared with bicycle exercise electrocardiography.

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Methods

STUDY GROUP

We studied 52 consecutive patients with chest pain, referred for coronary arteriography. Their age ranged from 25 to 77 years (mean 58±11 years); 38 were men, 14 were women. Fourteen patients had a previous myocardial infarction; seven had undergone previous balloon angioplasty. Patients with unstable angina, congenital or acquired valvular heart disease, cardiomyopathy, or previous cardiac surgery were excluded. To make this study similar to the clinical situation, we decided not to discontinue the medication before the dobutamine stress testing. Thirty-six patients were taking betablocking agents either alone or in combination with nitrates and/or calcium-channel blocking agents.

DOBUTAMINE STRESS TEST

Dobutamine was administered intravenously with an infusion pump, at incremental doses, up to a maximum of 40 $\mu g\, kg^{-1}\, min^{-1}$. In the first 30 patients we used steps of 5 $\mu g\, kg^{-1}\, min^{-1}$ for 3 min; in the last 22 patients the protocol was accelerated to steps of 10 $\mu g\, kg^{-1}\, min^{-1}$ for 3 min, and the maximal infusion rate was prolonged for another

3 min in negative studies. The ECG was continuously monitored (leads II, V_2 and V_5) and 12-lead ECG recording and cuff blood pressure measurement were obtained before and each minute during the test, up to 10 min after the end of the infusion. Computer averaging of the ECG signal was obtained by the Schiller System CSG/12. A ≥ 1 mm horizontal or downsloping ST segment depression occurring at 80 ms after the J point or an ST segment elevation were considered as an ischaemic response. End points of the test were: angina pectoris, severe hypertension ($\geq 230/130$ mmHg) or hypotension (fall ≥ 20 mmHg), arrhythmias (ventricular tachycardia or other life-threatening arrhythmias) and evident new wall motion abnormalities on the two-dimensional echocardiogram. Heart rate was not a criterion for termination. Metoprolol and sublingual nitrates were available as antagonists in case of prolonged chest pain or other major adverse effects.

ECHOCARDIOGRAPHIC STUDIES

The two-dimensional echocardiograms were performed with the patient in the left lateral decubitus position, using a commercially available wide angle phased array imaging system (Hewlett Packard Sonos 1000). Two-dimensional echocardiograms under resting conditions included all standard views, when possible. If a transducer position was coincident with one of the ECG precordial leads, the electrode was placed one intercostal space lower. During the test, new wall motion abnormalities were searched for in different views, by rapidly moving the transducer. Echocardiograms were continuously monitored during the provocative test and up to 10 min thereafter and recorded on video tape during the last minute of each step. Furthermore, both the studies under basal conditions and at the maximal dose of dobutamine were digitized on-line with a digital image acquisition system (PreVue III Nova Microsonics, ATL). This system allows the recording of one representative cardiac cycle obtained in the basal state and its storage in the memory of the system in a format eight cells deep; the procedure is repeated for each of four different views (in general, parasternal long- and short axis, apical 4- and 2-chamber views) and then stored again in a quad-screen format. At the maximal dose of dobutamine, four consecutive cardiac cycles for each view are similarly captured; the cycle with the best image quality is then selected and displayed side by side with the corresponding images at rest. Two different quad-screen formats containing the basal and peak images were finally stored on 5·25 inch, double-sided, high-density floppy disk and reviewed as a continuous loop at different play back speeds.

Two experienced observers, unaware of the results of the ECG or coronary angiography, reviewed all the video tapes and the digital images and reached a consensus on the grading of each study. For purposes of analysis, the left ventricle was divided into five segments: anterior, inferior and lateral walls, interventricular septum and apex. Both systolic wall thickening and inward motion were evaluated and according to a generally accepted qualitative analysis[6] left ventricular wall motion was graded as normal, hypokinetic, akinetic and dyskinetic; positivity of the test was linked to the development of new wall motion abnormalities. On this basis, a wall motion abnormality already present in basal conditions was not considered as a positive test.

BICYCLE EXERCISE TESTING

In 35 patients, symptom limited upright bicycle exercise test with stepwise increments of 20 Watts each minute was performed within 15 days of the dobutamine test. In the other 17 patients, the test was not performed because of contraindications (n = 7), or was performed either > 15 days apart from dobutamine stress echocardiography or during a different pharmacological treatment. We applied the same ECG recording system and the same criteria as that used for the dobutamine testing.

CORONARY ARTERIOGRAPHY

All patients underwent selective right and left coronary arteriography using the Judkins technique. The determination of coronary artery dimensions was performed with the computer-based Cardiovascular Angiographic Analysis System (CAAS), as already reported[7]. Briefly, boundaries of the relevant coronary artery segment are automatically detected from optically magnified and video digitized regions of interest of a selected single cine-frame angiogram. The diameter of the guiding catheter is used as a scaling device for size calibration. A computer estimation of the original arterial dimension at the site of obstruction is used to define the interpolated reference diameter. The interpolated percent diameter stenosis is then calculated and averaged from at least two projections. A vessel was considered to have significant obstruction if its diameter was narrowed by 50% or more.

STATISTICAL ANALYSIS

Values are reported as mean ± SD. The calculation of sensitivity, specificity and accuracy relied on the standard definition. Paired Student's t-test and McNemar's test were applied, when appropriate; P values <0.05 were considered significant.

Results

Some clinical data and the results of the dobutamine stress echocardiography, exercise ECG test and coronary arteriography in all the individual patients are presented in Table 1. Quantitative coronary measurements were performed in 31 patients; in the remaining 21 patients visual analysis was done, either because of normal coronary arteries (n = 6), diffuse coronary lesions and/or occlusion of the vessel (n = 8), or less than two projections on films (n = 7). Fifteen patients had normal or not significantly obstructed coronary arteries and 37 had significant coronary artery disease; of these patients, 20 had one-vessel, 10 had two-vessel and seven had three-vessel disease. The results of exercise ECG and dobutamine stress echocardiography in the study group are schematically displayed in Fig. 1.

Table 1 Results of dobutamine stress test, exercise test and coronary arteriography

Patient	Age	Sex	MI	bB	Dobutamine test: Dose (µg kg⁻¹ min⁻¹)	HR	SBP	r-WMA	n-WMA	ST (depression)	AP	Exercise test: WL	HR	SBP	ST (depression)	AP	Arteriography: LAD	LC	RCA
1	69	F	–	+	35	64	140	INF	IVS	–	–	100	95	130	V5-6	+	50	59	
2	59	M	–	+	30	84	120	–	IVS	–	–	160	122	160	II-III-V4/6	–	100	51	57
3	44	M	+	+	40	124	140	ANT	–	–	–	140	171	190	–	–	60		
4	67	M	+	+	40	72	115	INF	INF + LAT	–	–	100	116	140	–	–	64	65	
5	64	M	+	+	25	129	130	INF	INF	aVL-V2		160	155	190	–	–			54
6	45	M	–	+	35	96	130	–	INF	–	+	140	121	180	V4/6	+			100*
7	58	M	+	+	35	88	140	INF	INF + LAT	V3/6	+	not performed					> 50	> 50	> 50*
8	67	M	–	+	40	110	160	–	ANT	–	–	140	116	210	V3/5	+	62	64	
9	60	M	+	+	35	90	175	–	IVS	–	–	80	130	200	–	–	61		
10	68	F	–	+	40	70	155	–	–	–	–	80	135	180	–	–	24		18
11	54	F	–	+	35	94	115	–	IVS	–	–	140	169	180	V4-5	–		normal	
12	53	M	–	+	30	126	175	–	–	–	–	160	152	215	–	–		normal	
13	70	M	–	+	40	121	200	–	IVS	V4/6	+	not performed					64	66	62
14	64	F	–	+	40	99	220	–	–	–	–	100	83	140	–	–		normal	
15	75	M	–	+	35	101	160	–	INF + IVS	V4/6	–	not performed					> 50	100	100*
16	60	F	–	+	30	96	160	–	IVS	II-aVF-V5-6	–	60	95	150	II-III-aVF	–	100	> 50	> 50*
17	45	M	–	+	40	71	140	–	–	–	–	not performed					64	99	
18	77	F	–	+	40	80	140	–	–	–	–	60	128	170	V3/6	–	50	59	
19	56	M	–	+	40	92	130	–	–	–	–	120	111	160	–	–		59	
20	60	M	–	+	35	124	155	–	INF	–	+	60	116	180	V3/5	+	54	77	
21	42	M	+	+	40	70	115	INF + LAT	–	–	–	180	138	180	–	+	62	55	
22	65	M	+	+	40	116	130	INF	–	–	–	not performed					57	61	
23	52	M	–	+	40	78	190	–	–	–	–	140	100	220	–	–	47		34
24	61	F	–	+	40	61	110	–	–	–	–	80	97	160	–	–	16		
25	70	M	–	+	40	68	170	–	–	–	–	not performed					65		

26	38	M	–	+	40	64	195	–	–	–	–	180	115	170	–	–			55
27	52	F	–	+	40	69	130	–	INF	–	+	140	150	190	–	+			71
28	46	M	–	+	40	90	140	APEX	–	–	–	not performed					>90*		
29	49	M	–	+	40	120	135	APEX	–	–	+	not performed						55	
30	51	F	–	+	40	136	150	–	INF	V4/6	–	not performed						>50*	
31	71	M	+	+	40	104	110	IVS	–	–	–	not performed						66	
32	59	M	–	+	40	80	200	–	–	–	–	170	121	155	–	–	>50*		
33	50	M	+	+	40	90	190	–	INF	–	–	not performed					38	47	
34	56	M	–	+	40	119	140	–	ANT+IVS	–	+	120	126	180	V4/6	+	>50*		
35	45	M	–	+	40	120	140	–	–	–	–	90	115	160	–	+	100*		
36	68	M	–	+	40	97	135	–	–	–	–	not performed						<50*	
37	60	F	–	–	30	108	165	–	ANT+IVS	V4/6	–	80	167	220	II-III-aVF-V5-6	–	>50	>50	>50*
38	69	M	–	–	40	90	220	–	ANT+IVS	–	–	120	121	200	V4/6	–	>50*		
39	77	F	–	–	40	130	120	–	–	–	–	not performed						normal	
40	60	M	–	–	25	92	160	–	IVS+APEX	V5-6	+	100	101	170	II-III-aVF-V3/6	+	71		57
41	68	F	–	–	40	138	180	–	–	–	+	not performed					<50*		
42	60	F	–	–	40	100	180	–	INF	–	+	120	113	150	–	+		normal	
43	73	M	–	–	40	132	140	–	–	–	+	140	121	165	–	+	46		
44	58	M	+	–	40	156	160	IVS	–	–	–	160	172	190	–	–	100*		
45	49	M	+	–	40	151	165	–	–	–	–	not performed							62
46	46	M	–	–	40	125	200	–	APEX	–	–	180	137	190	–	–	51		
47	65	M	+	–	20	140	150	–	–	–	+	180	150	220	–	–	37		
48	38	M	+	–	35	115	115	INF+LAT	INF+LAT	–	+	160	155	145	V4-5	–	50	100	56
49	57	M	–	–	35	127	120	–	–	III (elevation)	–	180	139	225	–	–	54		100
50	25	M	–	–	40	134	120		–	–	–	not performed						normal	
51	72	F	–	–	40	125	150	–	–	–	–	not performed					41		
52	69	M	+	–	40	94	190	INF	–	–	–	80	119	215	–	–		100*	

MI = previous myocardial infarction; bB = betablocker therapy; HR = maximal heart rate (beats min⁻¹); SBP = maximal systolic blood pressure (mmHg), r-WMA = wall motion abnormalities at rest; n-WMA = new wall motion abnormalities; AP = angina pectoris; WL = maximal workload (Watts); IVS = interventricular septum; INF = inferior wall; LAT = lateral wall; ANT = anterior wall; LAD = left anterior descending artery; LC = left circumflex artery; RCA = right coronary artery. * = visual assessment of coronary arteriography.

The full dose of dobutamine was not given in 16 patients, primarily because of angina in six patients, evident new wall motion abnormalities in eight, short run of ventricular tachycardia in one, and ST segment elevation in one.

HAEMODYNAMIC RESPONSES

From the basal state to the peak effect of dobutamine, heart rate increased from 62 ± 10 beats min^{-1} to 102 ± 26 beats min^{-1} ($P<0.001$), while systolic blood pressure increased from 129 ± 19 mmHg to 149 ± 34 mmHg ($P=0.002$). Peak heart rate was higher in the 16 patients without than in the 36 patients with betablocker therapy (122 ± 20 vs 94 ± 21 beats min^{-1}, $P<0.0001$), while the difference in systolic blood pressure was not statistically significant (158 ± 30 vs 149 ± 28 mmHg).

DOBUTAMINE STRESS ECHOCARDIOGRAPHY

Analysis of the two-dimensional echocardiograms was possible in all patients both in basal conditions and during the infusion of dobutamine. When analysed separately, there was complete agreement between the results analysed from the video tape and from the digitized images on floppy disk.

In 13 patients an abnormal wall motion was present at rest; 10 of these had a documented previous myocardial infarction. A transient regional wall motion abnormality was detected during dobutamine stress echocardiography in 20 of the 37 patients with coronary artery disease (54%). All these patients had a significant stenosis in the coronary vessel supplying the regions that demonstrated wall motion abnormalities after dobutamine. Maximal heart rate and systolic blood pressure were similar when these 20 patients were compared with the 17 patients with significant coronary artery disease and a false-negative test (101 ± 20 vs 102 ± 28 beats min^{-1}; 153 ± 28 vs 148 ± 27 mmHg, NS), but patients with a positive test had a higher prevalence of multiple vessel disease (65% vs 35%). In five patients wall motion abnormalities developed at a dose of dobutamine $\leq 30\ \mu g\ kg^{-1}\ min^{-1}$, while in 15 patients a positive test was achieved at a dose $>30\ \mu g\ kg^{-1}\ min^{-1}$. Sensitivity of dobutamine stress echocardiography was highest in patients with diffuse coronary artery disease (Table 2); in particular, in all seven patients with three-vessel disease transient wall motion abnormalities were detected, compared to eight of the 20 patients with single vessel disease. The relation between the results of dobutamine stress echocardiography and the severity of coronary artery stenosis was assessed in 43 patients (Table 2); this group included 31 patients in whom coronary quantitative measurements were done and 12 patients with normal or occluded vessels. The prevalence of a positive test was directly correlated to the severity of the stenosis.

Of the 15 patients with <50% coronary stenoses, dobutamine stress echocardiography was positive in three (specificity = 80%); in all these patients the wall motion abnormalities occurred at a dose $\geq 35\ \mu g\ kg^{-1}\ min^{-1}$. Wall motion abnormalities were accompanied by symptoms in one patient. The overall diagnostic accuracy of dobutamine stress echocardiography was 62%.

We compared the results of dobutamine stress echocardiography in the subgroups of patients with and without betablocker therapy. No significant differences in sensitivity, specificity and diagnostic accuracy were found (54% vs 56%, 75% vs 86%, 62% vs 69%, respectively). However, the two groups were not comparable, since the patients on betablockers had a higher prevalence of coronary artery disease (78% vs 56%).

Diagnostic ST segment changes were induced by dobutamine in nine patients (24%) with significant coronary artery disease. Eight patients had ST segment depression and all developed new wall motion abnormalities. One patient with normal ECG at rest showed transient ST segment elevation in the inferior leads, without evident wall motion abnormalities. No patients with <50% coronary stenoses developed ST segment depression.

Angina pectoris occurred in 13 patients; nine of them had significant coronary artery disease. In eight of these nine patients, echocardiography was also positive.

EXERCISE ELECTROCARDIOGRAPHY TEST

In the 35 patients who performed both dobutamine echocardiography and exercise electrocardiography tests, peak heart rates and systolic blood pressures were significantly higher during exercise than during dobutamine (127 ± 23 vs 99 ± 24 beats min^{-1}, $P<0.0001$; 179 ± 25 vs 152 ± 30 mmHg, $P<0.0001$). ST segment depression occurred in 12 of the 26 patients with coronary artery disease and in one patient with normal coronary arteries, resulting in a sensitivity of 46% and a diagnostic accuracy of 57%. Concordant results with dobutamine echocardiography were present in 28 of these 35 patients (80%).

When comparing the results between dobutamine stress echocardiography and exercise electrocardiography in this subset of 35 patients, no statistically significant differences in sensitivity, specificity and accuracy were found (62% vs 46%, 67% vs 89%, 63% vs 57%, respectively). However, among the 26 patients with significant coronary artery disease, dobutamine stress echocardiography was positive in 16 and exercise ECG in 12 (Fig. 1); the difference was due to patients with single-vessel disease (Fig. 2).

ADVERSE EFFECTS OF DOBUTAMINE

Side effects during dobutamine occurred in 16 of the 52 patients (31%). None of these was severe and the test could be completed in all but one patient who developed a short run of ventricular tachycardia (three complexes) without wall motion abnormalities. Multiform premature ventricular beats and/or couplets occurred in eight patients. Junctional tachycardia developed in one patient and atrial fibrillation in another; both terminated spontaneously 3 min after the end of the infusion. One patient had nausea and a fall in blood pressure (30 mmHg) during the last step ($40\ \mu g\ kg^{-1}\ min^{-1}$). Chills immediately after

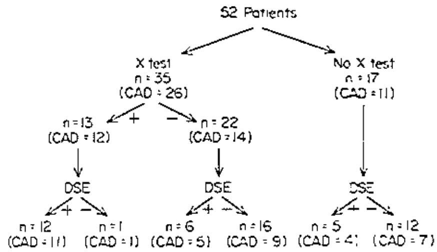

Figure 1 Outcome of exercise electrocardiography (X Test) and dobutamine stress echocardiography (DSE) in the study group. X Test = exercise testing performed, No X Test = exercise testing not performed. CAD = coronary artery disease (diameter stenosis ≥50%). DSE = dobutamine stress echocardiography. + = positive test, − = negative test.

Table 2 Results of dobutamine stress echocardiography according to the number of diseased vessels (number of vessels) and the severity of coronary artery stenosis (diameter stenosis)

	Number of patients	DSE+
Number of vessels		
0	15	3 (20%)
1	20	8 (40%)
2	10	5 (50%)
3	7	7 (100%)
Diameter stenosis		
<50%	13	3 (23%)
50–70%	18	7 (39%)
>70%	12	8 (67%)

DSE+ = patients with positive dobutamine stress echocardiography.

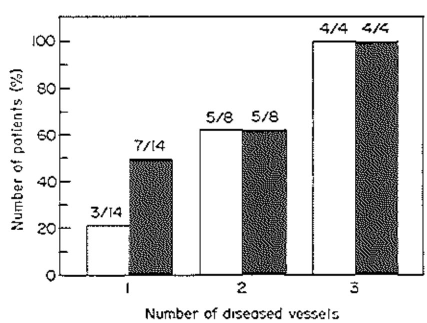

Figure 2 Prevalence of ischaemic response on exercise electrocardiography (open bars) and dobutamine stress echocardiography (closed bars) according to the number of vessels with ≥50% diameter stenosis.

the end of the infusion occurred in six patients and lasted at maximum 5 min. Intravenous metoprolol (5 mg) was given in five patients because of ST segment elevation, prolonged chest pain, or severe wall motion abnormalities, which were promptly reversed within 1 min.

Discussion

Dobutamine is a sympathomimetic drug which stimulates the $\beta1$-, $\beta2$- and $\alpha1$-adrenoreceptors in the cardiovascular system[5]. Clinically, it is used intravenously for short term treatment of acute congestive heart failure. Because of its pronounced inotropic effect and its chronotropic effect at higher doses dobutamine infusion can be used as a pharmacological stress test to induce myocardial ischaemia in patients with reduced coronary reserve[8]. Experimental data indicate that in the presence of severe coronary artery disease dobutamine can induce inhomogeneous perfusion leading to transient myocardial ischaemia[9–11]. This results in a wall motion abnormality which can be detected by two-dimensional echocardiography[12]. Some studies have indicated the clinical potential and usefulness of dobutamine to induce ischaemia. However, most of these studies used 12-lead ECG or scintigraphy to detect myocardial ischaemia[13–16], or included only post-myocardial infarction patients[17–19].

In our population of patients, dobutamine stress echocardiography offered diagnostic information similar to routine exercise electrocardiography for the diagnosis of myocardial ischaemia and was additive for its site and extent. In fact, the location of new wall motion abnormalities was always consistent with that of coronary artery disease, while it is well known that ST segment depression is not useful for identifying the site of ischaemia[20,21].

In the present study, including a group of symptomatic patients with and without myocardial infarction, the sensitivity of dobutamine stress echocardiography was 54%, with a specificity of 80%. The sensitivity was highest in patients with three-vessel disease (all had a positive dobutamine stress echocardiography) and in those with the most severe stenosis (>70%) (Table 2). This is consistent with previous results obtained with exercise and dipyridamole stress echocardiography[3,22,23]. The only previous reports to which the present results can be compared are those of Sawada *et al.* and Mazeika *et al*,[24,25] who, in similar groups of patients, found a slightly higher sensitivity (72% and 63%, respectively). The different results can be explained by several reasons, such as the prevalence of patients with multiple vessel disease, the method of analysis and the different cut-off for the definition of critical coronary artery stenosis, the different doses of dobutamine, and the concomitant use of therapy, especially betablockers. Therefore, if one also takes account of the small number of patients included in all the three studies, a fair comparison is difficult.

A potential major limitation in the present study is the use of betablockers in many patients, since they represent the antagonist of dobutamine. Therefore, from our results no conclusions can be drawn about the 'real' diagnostic accuracy of the test. In fact, to pursue this aim, patients should be studied after pharmacological wash-out. However, the present study is useful to assess the value of dobutamine stress echocardiography in the presence of the usual antianginal treatment, and also to compare its value to that of routine exercise ECG. We found that in patients without betablockers the sensitivity and specificity were similar to those in patients on betablockers. However, even here we cannot conclude that betablockers do not influence the accuracy of dobutamine stress echocardiography, since patients on betablockers had higher prevalence of coronary artery disease. Since patients on betablockers had a lower increment of heart rate after dobutamine, the addition of atropine, which has been proposed[26], could enhance the diagnostic accuracy by its chronotropic effect.

In agreement with Mazeika *et al.*[25], we found that dobutamine stress echocardiography provides the same information as that provided by exercise ECG as regards the diagnosis of myocardial ischaemia (ST segment depression and new wall motion abnormalities). This suggests that dobutamine stress echocardiography is a good alternative to exercise ECG in patients who are unable to perform exercise testing.

In contrast to previous findings[13–18], the dobutamine test had a very low sensitivity (24%) when only the ECG was considered. This can in part be due to the fact that in our protocol a new wall motion abnormality was considered as end-point, and it is well known that during myocardial ischaemia wall motion abnormalities occur early and before ST segment changes[27,28].

ANALYSIS OF FALSE-NEGATIVE RESULTS

Analyses of the patients with significant coronary artery disease and a negative dobutamine test (false negatives), reveals that these patients had a similar haemodynamic response to dobutamine, but a less diffuse coronary artery disease than those with a true positive test.

ANALYSIS OF FALSE-POSITIVE RESULTS

Transient wall motion abnormalities during the last step of the dobutamine infusion without electrocardiographic signs of ischaemia were seen in three patients who did not have significant coronary artery disease. In one, left ventricular hypertrophy was present, with a dilated left ventricle: the geometry of the left ventricular cavity and the altered loading induced by dobutamine could explain the wall motion abnormality. One woman with typical effort angina pectoris had a positive exercise test and normal coronary arteries, and in the last patient, dobutamine-induced transient wall motion abnormalities were seen in the inferior wall and a left circumflex coronary artery stenosis of 47% was found on the angiogram.

DIGITAL ACQUISITION TECHNIQUES AND STRESS ECHOCARDIOGRAPHY

Exercise echocardiography is a useful tool in the diagnosis of myocardial ischaemia. However, the excessive tachycardia and hyperventilation make it sometimes difficult to obtain good echocardiographic imaging at peak exercise or immediately after. In recent years, digital techniques have partially overcome this problem, allowing either on-line or off-line echo analysis. This seems to enhance the feasibility of stress echocardiography.

We have tested if cine loop analysis of dobutamine echocardiography offers advantages over the analysis of the images on video tape. Digital quad screen display gave the same information in terms of result of the test. Therefore, this technology is not strictly necessary for pharmacological stress echocardiography. However, the possibility of selecting one good cardiac cycle and to display the images in a quad screen format allows for a direct side by side comparison of the rest and peak studies, therefore making the analysis of the images faster and easier.

ADVANTAGES OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY

Dynamic exercise is the established modality of stress for the diagnosis and follow-up of patients with coronary artery disease: however, the value of exercise testing is limited in patients with musculoskeletal, neurological or pulmonary disease, in deconditioned patients or in patients for whom exercise is contraindicated. Moreover, elderly patients prior to major peripheral vascular surgery need a careful evaluation to identify high risk subgroups. The value of dipyridamole-thallium and dobutamine-thallium testing is well established[29–30], but this test requires high cost equipment not always readily available. In this setting, dobutamine stress echocardiography is a safe alternative for the screening for coronary artery disease and offers potential advantages to nuclear imaging.

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CHAPTER 9.

Pharmacological stress echocardiography in the diagnosis of coronary artery disease and myocardial ischaemia: a comparison between dobutamine and dipyridamole.

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Pharmacological stress echocardiography in the diagnosis of coronary artery disease and myocardial ischaemia: a comparison between dobutamine and dipyridamole

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KEY WORDS: Stress echocardiography, dobutamine, dipyridamole.

The objective of this study was to relate regional wall motion abnormalities assessed by dobutamine and dipyridamole stress echocardiography to quantitative measurements of coronary artery stenoses in consecutive patients referred for coronary angiography, and to compare haemodynamic effects of and complications related to the two agents.

Patients underwent stress echoes on separate days in random sequence and had coronary angiography within 3 days of stress echocardiography. Echocardiograms were assessed by two investigators unaware of the patients' coronary anatomy. Coronary angiograms were also assessed quantitatively using the computer-assisted Cardiovascular Angiography Analysis System.

There were 46 consecutive patients referred for coronary angiography; 28 were using β-antagonists.

Main outcome measures were sensitivity and specificity for dobutamine and dipyridamole stress echocardiography for detection of coronary artery disease (wall motion abnormalities at rest or stress) and myocardial ischaemia (stress induced new wall motion abnormalities).

Sensitivity for the detection of myocardial ischaemia was found to be 57% for dobutamine and 64% for dipyridamole. Specificities were 78% and 89% respectively. Sensitivities for detection of coronary artery disease (lesion ≥50% diameter stenosis) was 79% for dobutamine and 82% for dipyridamole; specificities were 78% and 89% respectively. These differences between the two agents are not significant. There were no severe side effects with either agent. Mean heart rate rose significantly with both tests but was higher with dobutamine; mean systolic blood pressure rose with dobutamine and fell with dipyridamole.

It was concluded that dobutamine and dipyridamole stress echocardiography have similar sensitivities and specificities for detection of myocardial ischaemia and coronary artery disease although the haemodynamic effects of the two agents are different. Both are free from serious complications.

Introduction

Coronary arteriography is still regarded as the gold standard for the diagnosis of coronary artery disease; however, the anatomical findings inadequately predict the physiological importance of obstructive lesions[1]. The functional significance of coronary artery stenoses may be assessed by 2-dimensional echocardiographic detection of left ventricular wall motion abnormalities induced by exercise[2], which is the established mode of stress for the assessment of cardiac function. Unfortunately, exercise cannot be performed by all patients; thus, alternative non-exercise stress has been proposed[3,4]. Both dobutamine and dipyridamole stress echocardiography have been reported to be useful in the diagnosis and prognostication of patients with suspected or proven coronary artery disease[5–7], but a direct comparison of their relative efficacy is still needed.

Accordingly, this study was designed to relate quantitative measures of coronary stenoses obtained by angiography to the presence of regional wall motion abnormalities as assessed by dobutamine and dipyridamole stress echocardiography in the same group of patients; in addition the haemodynamic consequences and side-effects of the two agents were assessed.

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Patients and methods

STUDY GROUP

Forty-six consecutive patients with suspected or known coronary artery disease, referred for coronary arteriography for the evaluation of chest pain, were prospectively enrolled in this study. Patients with unstable angina pectoris, previous cardiac surgery, congenital or valvular heart disease or documented cardiomyopathy were excluded.

All patients performed dobutamine and dipyridamole stress echocardiography on different days and in random sequence. The clinically prescribed medication was continued and was the same during the two stress echocardiographic tests: 28 patients were taking β-adrenergic blocking agents, either alone or in combination with nitrates and/or calcium channel blocking agents.

DOBUTAMINE STRESS TEST

An intravenous infusion of dobutamine was started at a dose of 5 or 10 μg kg^{-1} min^{-1} by means of an infusion pump and then increased in steps of 5 or 10 μg kg^{-1} min^{-1} every 3 min up to a maximum of 40 μg kg^{-1} min^{-1}. Electrocardiogram (ECG) was continuously monitored. A 12-lead ECG recording was obtained before and every minute during the test, up to 10 min after the end of the infusion; cuff blood pressure was measured every 2 min. Criteria for termination of the infusion were severe angina pectoris, severe hypertension (>230/130 mmHg) or hypotension (fall >20 mmHg of systolic blood pressure), ventricular tachycardia or obvious new wall motion abnormalities. Metoprolol and sublingual nitrates were at hand as antagonists.

DIPYRIDAMOLE STRESS TEST

Patients were instructed to avoid coffee and tea for at least 12 h before the test. Dipyridamole was administered intravenously at a dose of 0·84 mg kg^{-1} over 6 min, during continuous ECG monitoring. A 12-lead ECG was recorded before and every minute during the test and up to 20 min after the end of the infusion; cuff blood pressure was measured every 2 min. The infusion was stopped if the patient developed severe angina pectoris, obvious new wall motion abnormalities, hypotension or ventricular tachycardia. Aminophylline (200 mg) was injected in all the patients, at the peak ischaemic phase in the positive tests and 15 min after the end of the infusion in the negative ones.

For both stress tests, ST segment elevation or horizontal/down-sloping ST segment depression of more than 1 mm occurring at 80 ms after the J point were considered as an ischaemic response and an indication for stopping the test.

ECHOCARDIOGRAPHIC STUDIES

All the echocardiograms were performed using a commercially available wide-angle phased array imaging system (Hewlett-Packard Sonos 1000). Two-dimensional echocardiograms in the rest condition included all the conventional views. During the test, new wall motion abnormalities were sought in different views by rapidly moving the transducer. Echocardiograms were continuously monitored during the provocative tests and in the recovery phase and recorded on video tape at the end of each stage for the dobutamine, continuously during the dipyridamole stress test and at least every 2 min during the recovery phase in both tests.

The video tapes were analysed and a consensus was achieved by two observers, unaware of the symptomatic or ECG responses to the stress tests, clinical data or angiographic data. For purposes of analysis, the left ventricular wall was divided into a 16-segment model[8]. Both systolic wall thickening and inward motion were visually evaluated and wall motion was graded as 1 (normal), 2 (hypokinetic) 3 (akinetic) and 4 (dyskinetic). A wall motion score index was derived by averaging the individual scores for the segments graded. A stress echocardiographic test was considered positive for coronary artery disease if wall motion abnormalities were seen at rest and/or after stress; an ischaemic response was defined as a new wall motion abnormality, consisting of an increase from rest to peak study of at least one grade for any of the 16 segments analysed. In our laboratory, inter- and intra-observer variability for stress echocardiography are 0·91 ± 0·14 and 0·92 ± 0·20 respectively[9].

Table 1 Peak doses of dobutamine and dipyridamole used

Dobutamine peak dose (μg kg^{-1} min^{-1})	N	Dipyridamole peak dose (mg kg^{-1} 6 min^{-1})	N
20	1	0·42	1
25	2	0·56	2
30	3	0·67	1
35	8	0·72	1
40	32	0·84	41

QUANTITATIVE CINEANGIOGRAPHIC ANALYSIS

Coronary angiography was performed using the Judkins technique within 3 days of the stress echocardiographic tests. The coronary artery dimensions were determined with the computer-based Cardiovascular Angiography Analysis System (CAAS), as previously reported[10,11]. In brief, the boundaries of a selected coronary artery segment were detected automatically from optically magnified and video digitized regions of interest of a cineframe selected for analysis. The diameter of the coronary catheter was used for size calibration, comparing the mean diameter in pixels with the known size in millimetres. A computer estimation of the original arterial dimension at the site of obstruction was used to define the reference region. The interpolated per cent diameter stenosis was calculated by averaging the values from at least two angiographic views. A coronary artery narrowing of at least 50% diameter stenosis was considered significant.

STATISTICAL ANALYSIS

Data are expressed as means ± SD, unless specified. Where appropriate, 95% confidence intervals (CI) are given. The calculation of sensitivity, specificity and accuracy relied on the standard definition. Paired and unpaired t-tests were performed when appropriate to compare means calculated from continuous data. Discrete variables were compared using the chi-square test of association. A P value of less than 0·05 was considered significant.

Results

CLINICAL CHARACTERISTICS

Forty-six consecutive patients were studied; 32 were male, 14 female, with a mean age of 58 years (range 25–77 years). Fifteen patients had had a previous infarction and 28 were using β-antagonists at the time of the stress echoes. Doses of the stress agents used are shown in Table 1.

Table 2 Haemodynamic responses to dobutamine and dipyridamole

	Dobutamine	Dipyridamole	*P*
Peak HR (beats min^{-1})	102±24	87±16	0·0003
Peak SBP (mmHg)	151±30	122±23	<0·00001
Peak DBP (mmHg)	82·9±10·8	78·5±12·6	0·02

HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure.
Values are expressed as mean ± SD.

Quantitative coronary cineangiography was performed in 30 patients; in the remaining patients, quantitative analysis was not determined, either because of normal coronary arteries (eight patients) or diffuse lesions and/or total occlusion of the vessel (eight patients). Eighteen patients had normal or insignificantly diseased vessels (diameter stenosis <50%), while 28 patients had significant coronary artery disease; of these, seven had 3-vessel, 11 had 2-vessel and 10 had single-vessel disease. Of the 28 patients with significant coronary artery disease, 16 had normal left ventricular wall motion at rest (group A) and 12 had wall motion abnormalities at rest (group B); 10 of these 12 had a previously documented myocardial infarction.

Neither dobutamine nor dipyridamole caused any serious complications. Mild symptoms such as palpitations, headache, cold or heat, dizziness, flushing and mild dyspnoea were present in 17 patients and these symptoms disappeared after infusions were stopped. There was no difference between the agents with regard to the incidence of these side-effects.

HAEMODYNAMIC RESPONSES (TABLE 2)

From the rest state to the peak effect of dobutamine, heart rates increased from 68±14 beats min^{-1} to 102±24 beats min^{-1} ($P<0·00001$), systolic blood pressure increased from 131±23 mmHg to 151±30 mmHg ($P<0·00001$), while diastolic blood pressure did not change significantly. During infusion of dipyridamole, heart rates increased from 68±12 to 87±16 beats min^{-1} ($P<0·00001$), systolic blood pressure remained unchanged while diastolic blood pressure decreased slightly (from 81·4±11·3 mmHg to 78·5±12·6 mmHg ($P=0·03$). At the peak effect, heart rates and systolic blood pressure were significantly higher after dobutamine than after dipyridamole ($P=0·0003$ and $P<0·00001$ respectively).

STRESS ECHOCARDIOGRAPHY IN THE DIAGNOSIS OF MYOCARDIAL ISCHAEMIA (TABLE 3)

Dobutamine stress echocardiography revealed new wall motion abnormalities in 16 of 28 patients with coronary artery disease, a sensitivity of 57%, 95% CI 37–76%. Of these 28, new wall motion abnormalities occurred in 10 of 16 (63%) with normal wall motion at rest (group A), and in six of 12 (50%) patients with a resting wall motion abnormality (group B). New wall motion abnormalities occurred during dipyridamole stress echo in 18 of 28 patients with coronary artery disease, a sensitivity of 64%, 95% CI 44–81%. Of these 28, new wall motion abnormalities occurred in 12 of 16 (75%) patients from group A and in six of 12 (50%) from group B. These sensitivities for the two stress agents are not significantly different.

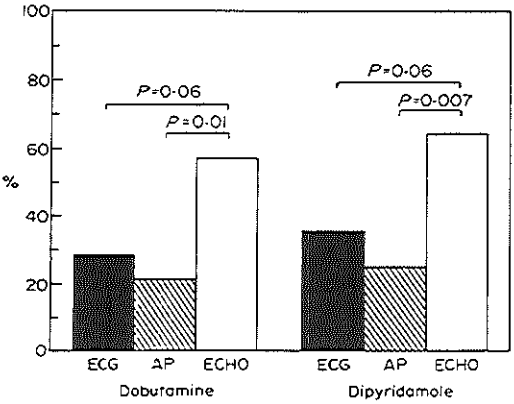

Figure 1 Occurrence of ST segment depression (ECG), angina pectoris (AP) and new wall motion abnormalities (ECHO) in the 28 patients with significant coronary artery disease during dobutamine (left) and dipyridamole (right) stress echocardiography.

The specificity for dobutamine stress echo was 78%, 95% CI 52–94% (four of 18 patients without significant coronary artery disease had a positive test), and for dipyridamole the specificity was 89%, 95% CI 65–99% (two of 18 patients had a positive test with dipyridamole); these specificities are not significantly different.

Sensitivities of echocardiographic changes, electrocardiographic changes and angina pectoris after dobutamine and dipyridamole are shown in Fig. 1. Of the 28 patients with significant coronary artery disease, typical ST segment changes were found in eight after dobutamine and in 10 after dipyridamole. During dobutamine, one patient with an occlusion of the right coronary artery and a mild stenosis on the left anterior descending coronary artery showed an ST segment elevation in an inferior lead, without obvious changes in wall motion. Angina pectoris was present in six patients and seven patients respectively. New or increased wall motion abnormalities showed higher sensitivity than ECG changes and angina pectoris ($P=0·01$ between angina and echo during dobutamine and $P=0·007$ between angina and echo during dipyridamole; $P=0·06$ between ECG and echo in both tests).

Four patients without significant coronary artery disease developed angina pectoris and in one there were ST segment changes with dobutamine, while in five patients either ST segment changes or angina pectoris was found after dipyridamole.

The effect of the number of abnormal vessels present on the ability to obtain an ischaemic response revealed by

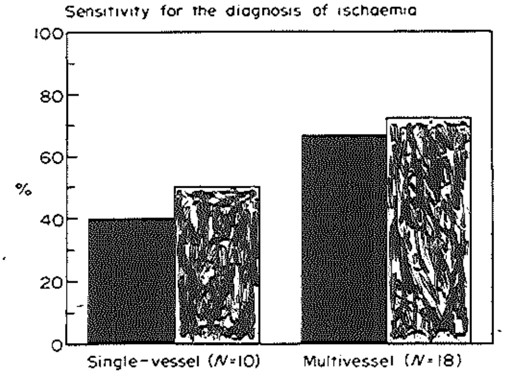

Figure 2 Comparison of the sensitivities for the diagnosis of myocardial ischaemia between dobutamine (solid bars) and dipyridamole (open bars) stress echocardiography in patients with single- and multivessel disease.

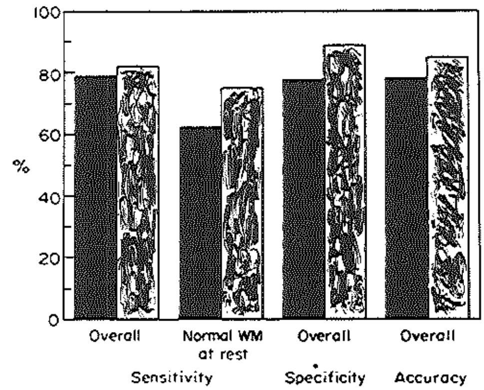

Figure 3 Specificity, sensitivity and accuracy for the diagnosis of coronary artery disease of dobutamine (solid bars) and dipyridamole (open bars) stress echocardiography. WM = walls motion.

2-dimensional echocardiography is shown in Fig. 2; in patients with single-vessel disease, sensitivity was 40% (four of 10) for dobutamine compared with 50% (five of 10) for dipyridamole, while for patients with multivessel disease the sensitivities were 67% (12 of 18) and 72% (13 of 18) respectively.

Of 28 patients using β-antagonists, 20 had coronary artery disease and eight no significant coronary disease. New wall motion abnormality occurred in 11 of 20 (55%) during dobutamine and in 14 (70%) during dipyridamole; the specificities were 75% (six of eight) and 88% (seven of eight) respectively. In this subgroup of patients, the mean dose of dobutamine was the same as in patients off therapy.

STRESS ECHOCARDIOGRAPHY IN THE DIAGNOSIS OF CORONARY ARTERY DISEASE

Since the diagnosis of coronary artery disease by 2-dimensional echocardiography is based on the presence of segmental wall motion abnormalities at rest, as well as stress-induced wall motion abnormalities, the overall sensitivity for the diagnosis of coronary artery disease was superior to that for the diagnosis of myocardial ischaemia (79% *vs* 57% for dobutamine; 82% *vs* 64% for dipyridamole). The specificity and accuracy are also represented in Fig. 3.

DIAGNOSTIC COMPARISON OF DOBUTAMINE AND DIPYRIDAMOLE STRESS ECHOCARDIOGRAPHY

In patients with significant coronary artery disease, the wall motion score index increased significantly from the rest to the stress study both during dobutamine and dipyridamole, and the values during stress were similar ($1{\cdot}32 \pm 0{\cdot}26$ *vs* $1{\cdot}31 \pm 0{\cdot}23$, not significant) (Fig. 4).

In the coronary artery disease group, both stress echocardiographic studies were abnormal (new wall motion abnormality) in 13 patients and normal in seven patients; in 16 of 18 patients with multivessel disease, wall motion

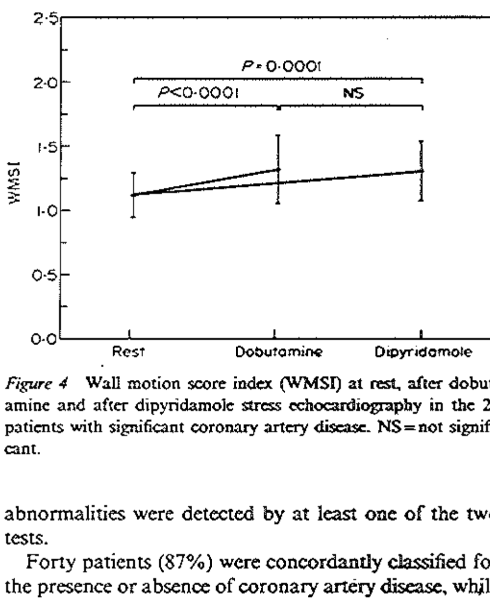

Figure 4 Wall motion score index (WMSI) at rest, after dobutamine and after dipyridamole stress echocardiography in the 28 patients with significant coronary artery disease. NS = not significant.

abnormalities were detected by at least one of the two tests.

Forty patients (87%) were concordantly classified for the presence or absence of coronary artery disease, while the agreement for the diagnosis of myocardial ischaemia was 78% (36 of 46). Furthermore, the same ventricular walls were involved by ischaemia in the 13 patients with both positive tests. A segment-by-segment comparison of dobutamine and dipyridamole stress echocardiography showed concordance in 690 of a total of 736 (94%) segments, and in 85 of 99 (86%) segments affected in one or both tests (Fig. 5).

QUANTITATIVE STENOSIS MEASUREMENTS

The relation of new wall motion abnormalities induced by dobutamine and dipyridamole to quantitative measurements of coronary stenosis is represented in Fig. 6. Patients

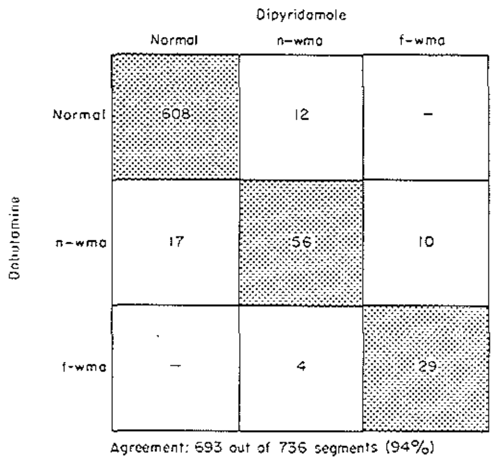

Figure 5 Agreement between dobutamine and dipyridamole stress echocardiography in the segmental analysis of left ventricular wall motion. Normal = normal wall motion at rest and after stress, n-wma = new wall motion abnormalities, f-wma = wall motion abnormalities at rest without new or worsening wall motion abnormalities after stress ('fixed').

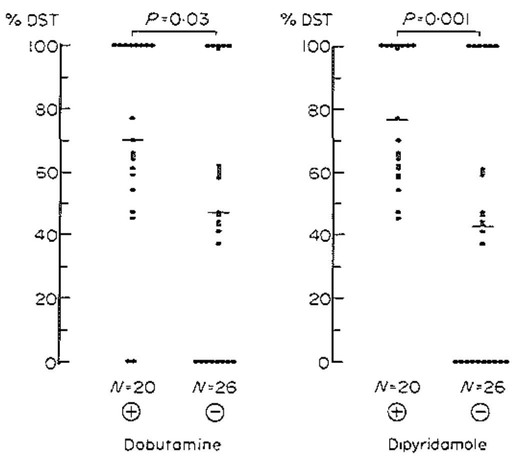

Figure 6 Comparison of per cent diameter coronary stenoses (%DST) between patients with and without new wall motion abnormalities (NEW WMA) during dobutamine (left) and dipyridamole (right) stress echocardiography.

with an ischaemic response had more severe coronary stenoses compared to those with a non-ischaemic response: mean (±SD) per cent diameter stenosis of the most severely affected coronary arteries for those with new wall abnormalities with dobutamine was 70±31 compared with 47±38 for those without new wall motion abnormalities ($P=0·03$), and for dipyridamole the corresponding values were 76±21 compared with 42±40 ($P=0·001$). However, the prediction of the severity of coronary stenoses in individual patients was limited, since patients with comparable per cent diameter stenosis frequently had discordant responses with both tests.

Discussion

In this study we made a direct comparison of dobutamine with dipyridamole in conjunction with 2-dimensional echocardiography for the detection of significant coronary artery disease and myocardial ischaemia. Patients were studied in a random sequence on different days with the two modalities. Sensitivity and specificity did not significantly differ between the two stress tests and the 95% confidence intervals are similar.

The most important mechanism involved in the development of ischaemia caused by dipyridamole is the maldistribution of flow, mostly from subendocardium to subepicardium[12]. However, due to the increase in heart rate, the increase in rate-pressure product might also play a role in precipitating ischaemia[13]. In contrast, the mechanism of ischaemia caused by dobutamine is primarily based on the increase in myocardial oxygen demand, secondary to the positive inotropic and chronotropic effects[14]. Despite the different mechanisms involved and the experimental evidence that dobutamine should be more suitable than dipyridamole for the detection of new wall motion abnormalities[15], the present study showed a very good correlation between the results of stress echocardiography with the two pharmacological stress agents. The apparent discrepancy with data from Fung *et al.*[15] may be due, in part, to the submaximal dose of dipyridamole that was employed in their experimental study. Indeed, it is well demonstrated that a high dose of dipyridamole (0·84 mg kg^{-1} in 10 min) increases the sensitivity of the test, with no loss in specificity[13]. This suggests that, independent of the mechanism, dobutamine and dipyridamole in high doses have a similar potential to induce ischaemia in the presence of critical coronary stenoses.

Pharmacological stress tests, either in conjunction with 2-dimensional echocardiography or with nuclear imaging, have been proven to be of value in the diagnosis and prognosis of patients with coronary artery disease[16–18]. However, the finding of significant coronary lesions by visual analysis of angiograms is of limited value in predicting the physiological importance of the stenosis[1]. This is due to reproducibility errors[19,20], and also to other factors such as the site and the length of the lesion and the presence of collateral vessels.

Wilson *et al.*[21] observed that in patients with isolated coronary artery lesions, coronary flow reserve is related to quantitative angiographic measures of lesion severity; patients with abnormal coronary flow reserve had a mean diameter stenosis of 70% in comparison to patients with normal coronary flow reserve who had a mean value of 45%. This point has been very recently underscored by Sheikh *et al.*[2]; they found a relationship between coronary stenoses assessed quantitatively and wall motion

Table 3 Results of dobutamine and dipyridamole stress echocardiography

		N	Rest WMA	New WMA	Positive test
Dobutamine	No CAD	18	0	4 (22%)	4 (22%)
	CAD	28	12 (43%)	16 (57%)	22 (79%)
	group A	16	0	10 (63%)	10 (63%)
	group B	12	12 (100%)	6 (50%)	12 (100%)
Dipyridamole	No CAD	18	0	2 (11%)	2 (11%)
	CAD	28	12 (43%)	18 (64%)	23 (82%)
	group A	16	0	12 (75%)	12 (75%)
	group B	12	12 (100%)	6 (50%)	12 (100%)

CAD = coronary artery disease, No CAD < 50% diameter stenosis, WMA = wall motion abnormalities, N = number of patients, group A = normal wall motion at rest, group B = abnormal wall motion at rest, positive test = abnormal wall motion at rest and/or after stress.

abnormalities detected by exercise echocardiography in patients with isolated, single-vessel disease. The results of the present study are partially in agreement with those findings, showing that in a series of consecutive patients with chest pain referred for coronary angiography the severity of coronary stenosis was higher in patients with an ischaemic response to pharmacological stress. However, the presence of stress-induced myocardial ischaemia was unpredictable based on the severity of the coronary stenoses. This is not surprising, since the present study did not deal with patients with discrete single coronary lesions, but with a heterogeneous population, including patients with previous myocardial infarction and or wall motion abnormalities at rest, diffuse coronary lesions and coronary collateral vessels.

STUDY LIMITATIONS

This study may be criticized on the basis of its small sample size being inadequate to show significance in the trend in favour of the dipyridamole test. However, even if this trend continued, a study population of several hundred patients would be required to show significance, and ethically we feel unjustified in subjecting these patients who often have significant coronary artery disease to two stress tests.

An additional limitation of this study is the presence of β-antagonists in 28 of these 46 patients. This blockade, in effect, represents the antidote to dobutamine and we initially considered that the continuation of β-blockers could have underestimated the value of dobutamine in favour of dipyridamole stress echocardiography although recent data indicate that the β-blockade also affects the dipyridamole test[22]. Subgroup analysis showed similar sensitivity and specificity for those with and without β-blockers, although the numbers in the subgroups were small and the analysis was performed retrospectively. This finding is in agreement with data by Sawada *et al.*[23], and may be due to the presence of more severe coronary artery disease in those patients who were treated with β-blockers. Indeed, the prevalence of multivessel disease among the population of the present study was 45% in patients treated, compared to 27% in patients off therapy. Ideally a direct comparision of the physiological effects of these two agents would require assessment in patients off therapy, but this may be clinically impractical in such a patient population. Moreover, β-blocker therapy may also mask the side-effects profile of dobutamine, lowering the incidence of arrhythmias, for instance.

Finally, we used a high dose for both stress echocardiographic tests. However, we employed dipyridamole in an unconventional time interval of 6 min, rather than in the standard stepwise model[13]. Although no patient had any serious complications, the safety of 'one-shot' administration remains to be assessed.

RELATION TO PREVIOUS CLINICAL STUDIES

The results of this study are in agreement with those obtained by other authors. In fact, Previtali *et al.*[24] found an overall sensitivity of 68% for dobutamine and 57% for dipyridamole in a population off therapy. Dipyridamole stress echocardiography showed the same sensitivity as dobutamine in patients with multivessel disease (92%) and a lower senstivity, in single vessel disease (31 *vs* 50%) although the difference was not statistically significant. In patients studied by dobutamine stress echocardiography after acute myocardial infarction, Mannering *et al.*[25] observed new or increased wall motion abnormalities in 20 of 41 patients and Berthe *et al.*[6] in 13 of 30 patients; these values are similar to the 50% rate of positive tests in patients with wall motion abnormalities at rest found in the present study. Picano *et al.* found new wall motion abnormalities during dipyridamole stress echocardiography in 74% of 72 patients with coronary artery disease. Seventeen of these patients had a previous myocardial infarction with wall motion abnormalities at rest; when baseline and dipyridamole-induced wall motion abnormalities were both included, the sensitivity for the diagnosis of coronary artery disease increased to 81%[13], compared to 82% in our study.

Typical ST segment changes and/or angina were less frequent than in other studies[6,14,17,25–28]. However, many of the patients in this series were being treated with β-blockers which might influence the electrocardiographic response, as indicated by clinical and experimental data[29,30]. Furthermore, in the development of myocardial ischaemia transient wall motion abnormalities occur before ECG changes and angina[31]; since wall motion abnormalities were considered as an endpoint, it might be possible that in some patients ischaemia was not prolonged enough to induce ST segment changes.

In conclusion, for patients on antianginal therapy, dobutamine and dipyridamole stress echocardiography provide similar diagnostic information on the presence of myocardial ischaemia. Further studies are required to assess if the same results are obtained in patients off medication.

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CHAPTER 10.

Simultaneous dobutamine stress echocardiography and technetium-99m isonitrile single-photon emission computed tomography in patients with suspected coronary artery disease.

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Simultaneous Dobutamine Stress Echocardiography and Technetium-99m Isonitrile Single-Photon Emission Computed Tomography in Patients With Suspected Coronary Artery Disease

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Objectives. The purpose of this study was to determine the relative value of dobutamine stress echocardiography and technetium-99m isonitrile single-photon emission computed tomography (mibi SPECT) in the detection of myocardial ischemia.

Background. Stress-induced new wall motion abnormalities and transient perfusion defects are both used for the diagnosis of myocardial ischemia.

Methods. One hundred five consecutive patients with either proved or suspected coronary artery disease, who were referred for perfusion scintigraphy, were studied by a combination of the two techniques. Both echocardiographic and mibi SPECT images were visually analyzed. Three patients were excluded from the final analysis because of unsatisfactory examinations: two with noninterpretable stress echocardiograms and one with noninterpretable mibi SPECT images. The response to stress was concordantly classified by both techniques in 68% of patients (kappa = 0.51).

Results. Dobutamine stress echocardiography revealed the presence of ischemia in 38 and mibi SPECT in 45 patients (overall agreement = 74%, kappa = 0.46). The agreement was higher in patients without previous myocardial infarction (84%, kappa = 0.62). When regional analysis was performed, concordance of stress echocardiography and mibi SPECT occurred in 84% of the 306 regions (kappa = 0.45). Regional agreement was also slightly higher in patients without previous infarction (88%, kappa = 0.50). In 21 patients without previous myocardial infarction who underwent coronary angiography, the overall sensitivity of dobutamine stress echocardiography and mibi SPECT for the diagnosis of coronary artery disease (diameter stenosis >50%) was 75% and 83%, respectively, with a specificity of 89% (eight of nine patients) for both tests.

Conclusions. Dobutamine stress echocardiography represents a reasonable alternative to dobutamine mibi SPECT for the functional assessment of patients with suspected myocardial ischemia and without previous myocardial infarction.

(J Am Coll Cardiol 1993;21:1591–6)

The noninvasive detection of myocardial ischemia remains an important clinical problem. Numerous methods have been introduced to induce ischemia, such as exercise testing (1–3), pharmacologic stress using dipyridamole, dobutamine (4–6) or atrial pacing (7). Ischemia may be detected using the electrocardiogram (ECG), perfusion scans (8,9) or echocardiography (10–12). The diagnostic accuracy of the stress ECG alone is limited. Nuclear perfusion studies give accurate results but are expensive. By comparison, stress echocardiography is a widely available, a relatively cheap method for detecting myocardial ischemia, and it has been the subject of increasing interest and use in different clinical settings, such as detection of coronary artery disease (5,13), assessing the results of interventions (14) or predicting perioperative cardiac risk (15–17). Dobutamine is a beta-adrenergic agonist with positive inotropic and chronotropic effects. These properties make it suitable for inducing myocardial oxygen demand and provoking myocardial ischemia in cases of coronary stenosis. Pharmacologic stress imaging with dobutamine has recently been used in conjunction with both thallium scintigraphy and echocardiography (8). With both, dobutamine provided good diagnostic accuracy for the presence of coronary artery disease. However, no study has been performed for comparing the diagnostic merit of the two methods. In addition, no comparative study has been carried out with technetium-99m isonitrile (mibi). In particular, recent reports have demonstrated that dobutamine stress echocardiography has a good diagnostic accuracy for the diagnosis of coronary artery disease, which is similar to

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that obtained with dobutamine thallium scintigraphy (5,8). However, the recent introduction of single-photon emission computed tomography (SPECT) has improved the diagnostic accuracy of scintigraphic technique for the detection of myocardial ischemia and mibi has contributed to improve the image quality of tomographic studies (9,15,18). So far, the agreement between dobutamine-induced wall-motion abnormalities (detected by echocardiography) and transient perfusion defects (detected by mibi SPECT) for the diagnosis and localization of myocardial ischemia has not been explored.

Accordingly, the aim of this study was to establish the correlation between the two tests in a consecutive group of patients with chest pain and proved or suspected coronary artery disease who underwent simultaneously performed dobutamine stress echocardiography and mibi SPECT.

Methods

Study patients. The study group consisted of 105 consecutive patients referred to the nuclear cardiology laboratory at the Thoraxcenter for the evaluation of suspected myocardial ischemia. Their ages ranged from 24 to 81 years (mean ± SD 62 ± 12); 58 were men and 47 women. Fifty-nine patients had a previous myocardial infarction. At the time of the study, 55 patients were receiving beta-adrenergic blocking agents administered either alone or in combination with nitrates or calcium channel blocking agents, or both.

Dobutamine stress echocardiography. After the patients gave written informed consent, two-dimensional precordial echocardiography was performed. Standard parasternal and apical views were recorded on videotape. Dobutamine stress echocardiography was performed according to a previously described protocol (11). Dobutamine was infused through an antecubital cannula starting at a dose of 10 μg/kg per min, increasing by 10 μg/kg every 3 min to a maximum of 40 μg/kg per min, which was continued for 6 min. In patients not achieving 85% of age-predicted maximal exercise heart rate, atropine (up to 1 mg) was given intravenously if necessary with the continuation of dobutamine.

The ECG was continuously monitored throughout dobutamine infusion, 12-lead ECG recorded each minute and cuff blood pressure taken every 3 min. Two-dimensional echocardiogram was continuously monitored and was recorded on videotape for the last minute of each stress stage and continuously after atropine administration. The infusion was stopped if the patient developed an obvious new wall motion abnormality, ST segment depression >2 mm 80 ms after the J point, ST segment elevation, ventricular tachycardia or any complication considered to be due to dobutamine. Metoprolol was available and used to reverse the effects of dobutamine or atropine if these did not revert spontaneously and quickly.

The assessment of echocardiographic images was performed by two experienced investigators after acquisition without knowledge of the patients' clinical data or coronary anatomy but with knowledge of the doses of dobutamine and atropine used. When there was disagreement between the two off-line assessors, a third investigator viewed the images without knowledge of the previous assessments and a majority decision was achieved. For this semiquantitative assessment, the left ventricular wall was divided into 14 segments, as described by Edwards et al. (19) and scored using a 4 point scale: 1 = normal, 2 = hypokinetic, 3 = akinetic and 4 = dyskinetic. To analyze wall motion, images recorded on videotape were subsequently reviewed at various playback speeds. Both systolic wall thickening and inward wall motion were visually evaluated. An increase in score between rest and stress in one or more segments, that is, a new or worsened wall motion abnormality, constituted a positive test. In our laboratory both inter- and intraobserver agreement for stress echocardiographic assessment are 91% (20); recent data indicate that assessment of 100 stress echocardiograms is adequate training for diagnostic accuracy in this technique (21), and all investigators in our center have such experience. We did not use a continuous loop format for assessment of pharmacologic stress echocardiography in all patients because we have previously tested whether cine loop analysis of dobutamine echocardiography had advantages over analysis of images from video tape and found the same results by the two techniques (10).

Mibi SPECT imaging at rest and at peak stress. Approximately 60 s before termination of the stress test, an injection of 370 MBq of ^{99m}Tc mibi was administered. The stress mibi SPECT images were acquired, on average, 1 hour after dobutamine ended. Thirty-two projections (180° scanning) were obtained with an acquisition time of 45 s/projection. For each patient, six oblique (short-axis) slices were defined from the apex to the base and three sagittal slices from the septum to the lateral wall. For rest studies, patients were injected with 370 MBq of ^{99m}Tc mibi at least 24 h after the first study using the same protocol. One experienced observer visually assessed the uptake of radiotracer in studies both at rest and during exercise, giving a semiquantitative score based on a scale of 4 grading (1 = normal, 2 = decreased uptake, 3 = severely decreased uptake, 4 = absence of uptake). A persistent perfusion defect was defined when a score ≥2 in one or more segments was present both during exercise and at rest. Moreover, it was decided in advance to consider a nonreversible defect of the septal segments in the two basal short-axis slices as normal (four segments). A perfusion defect was considered reversible when the score at rest improved by at least one grade with respect to the exercise scan in two or more contiguous segments. A significant but incomplete improvement of perfusion from the exercise to the rest scan (persistence of at least one segment with a score ≥2 in the scan at rest) was regarded as an ischemic response and, for the purpose of data analysis, was classified as a reversible defect.

For each technique, three different responses to stress were defined: normal (absence of rest and stress abnormalities), ischemic (reversible scintigraphic perfusion defects and transient wall motion abnormalities during stress echocardiography) and fixed abnormalities—infarction (fixed scintigraphic perfusion defects, echocardiographic wall motion abnormalities at rest without worsening at peak stress). When both reversible and fixed defects were present, the response was classified as ischemic. To allow a valid comparison of each technique in localizing ischemia, the 47 segments of the left ventricle on SPECT and the 14 echocardiographic segments were grouped into the following six major regions: anterior, posterior, lateral, interventricular septum (subdivided in anterior and posterior septum) and apex. Furthermore, for analysis of regional agreement the six major regions were further grouped into three myocardial areas: 1) anterior and septal, 2) posterior and lateral, and 3) apical. For analyzing reasons for discrepancies, the original six-region model was used to detect adjacent abnormalities. The results obtained by the two methods were then compared.

Coronary angiography. Coronary angiograms using the Judkins technique were performed within 3 months in 71 patients. Significant coronary artery disease was defined as a diameter stenosis >50%.

Statistical analysis. All continuous variables are expressed as mean value ± SD. The agreement between mibi SPECT and stress echocardiography was defined as the percent of concordant diagnoses and was also assessed by calculating the kappa value; kappa values between 0.75 and 1 were considered indicative of good agreement, those between 0.40 and 0.75 indicative of moderate agreement and those between 0 and 0.40 indicative of poor agreement. McNemar's test was used to compare the percent of concordant diagnoses between paired data (22). A p value < 0.05 was considered significant.

Results

Feasibility of dobutamine stress test. The dobutamine stress test was completed without serious complications in all patients. The clinical variables of patients are shown in Table 1. In the study group, 66 patients reached 85% of the age-predicted maximal exercise heart rate. On average, the heart rate achieved was 88% compared with the theoretic maximal exercise heart rate of these 66 patients; 28 patients required atropine to reach the target heart rate. Three patients were excluded from final analysis: two because of technically inadequate echocardiograms at peak stress and one patient because of poor quality mibi SPECT images (liver uptake interfered with myocardial uptake). Thus, 102 of 105 patients had analyzable data with both tests and were included in the study. The overall success rate of the study was 98%; no patient was excluded from analysis on the basis of poor image quality on the rest echocardiogram. In 13 patients, because parasternal views were inadequate, only the apical views were analyzed; however, all segments were visualized in at least one view.

Table 1. Results of Dobutamine Stress Test

Rest heart rate (beats/min)	70 ± 13
Peak heart rate (beats/min)	131 ± 16
Rest systolic blood pressure (mm Hg)	138 ± 22
Rest diastolic blood pressure (mm Hg)	81 ± 18
Peak systolic blood pressure (mm Hg)	151 ± 26
Peak diastolic blood pressure (mm Hg)	78 ± 10
Rate-pressure product (rest)	9,725 ± 2,500
Rate-pressure product (peak)	19,798 ± 4,311
Peak theoretical maximal exercise heart rate (%)	88 ± 13
Chest pain (no.)	35
ST segment depression (no.)	21
ST segment elevation (no.)	7
Atropine used (no.)	44

Data are expressed as mean value ± SD or number of patients.

Relations between wall motion and myocardial perfusion. The results of dobutamine echocardiography and dobutamine mibi SPECT in the 102 patients are presented in Figure 1. Echocardiography revealed new wall motion abnormalities in 38 patients and wall motion abnormalities at rest without further worsening at peak stress in 31 patients; test results were negative in 33 patients. On mibi SPECT, reversible perfusion defects were detected in 45 patients, and fixed perfusion defects alone in 28; the test results were negative in 29 patients. The two methods concordantly classified 69 patients (68%, kappa = 0.51). The majority of discrepancies were due mainly to pattern discordance in which both tests showed an abnormal pattern but the type of abnormality was different, that is, rest wall motion abnormality versus reversible perfusion defect (11 patients) or new wall abnormality versus fixed perfusion defect (8 patients). In these 19 patients, both tests were definitely abnormal but, by definition, the results were discordant.

For detection of presence or absence of myocardial

Figure 1. Results of simultaneous dobutamine echocardiography (ECHO) and ^{99m}technetium isonitrile single-photon emission computed tomography (SPECT). Squares marked 24, 28 and 17 display number of patients concordantly classified by both methods. "Infarction" = a rest wall motion abnormality without further worsening during stress on echocardiography and a fixed perfusion defect on SPECT; "Ischemia" = a new wall motion abnormality on echocardiography and a reversible perfusion defect on SPECT.

SPECT \ ECHO	Normal	"Ischemia"	"Infarction"
Normal	24	2	3
"Ischemia"	6	28	11
"Infarction"	3	8	17

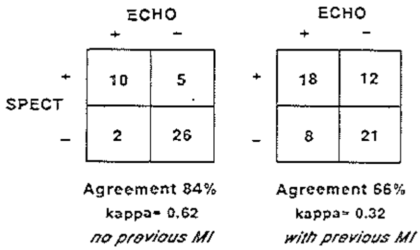

Figure 2. Agreement for ischemia between dobutamine echocardiography (ECHO) and ^{99m}technetium isonitrile single-photon emission computed tomography. The agreement is higher in patients without previous myocardial infarction (MI) (left panel).

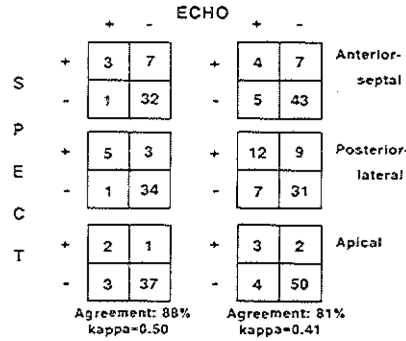

Figure 3. Regional agreement for ischemia between dobutamine echocardiography (ECHO) and ^{99m}technetium isonitrile single-photon emission computed tomography (SPECT) in 306 regions. The set of 2 × 2 tables at left represents data of patients without previous myocardial infarction, and the row at right represents data of those without previous myocardial infarction. The agreement was slightly higher in patients without infarction.

ischemia (that is, new wall motion abnormalities and reversible perfusion defects), the overall agreement between the two methods was 74% (75 of 102 patients, kappa = 0.46). The agreement increased when we separately analyzed data of patients without previous myocardial infarction (84%, kappa = 0.62, Fig. 2). The specific reasons for discrepancies in patients with normal wall motion at rest are reported in Table 2. Of seven patients, three had a different but abnormal pattern (ischemia versus infarction), whereas four patients with an ischemic response on one test were classified as normal on the other test.

The overall regional agreement was 84% (kappa = 0.45). Slightly better agreement was found if we again separated the group without previous infarction from that with previous infarction (88%, kappa = 0.50; 81%, kappa = 0.41, respectively, Fig. 3). Altogether, 50 areas were found with diverging results, 16 areas in 43 patients without previous myocardial infarction and 34 areas in 59 patients with previous infarction. In 19 areas the two methods showed a discordant pattern (new wall motion abnormalities vs. fixed perfusion defects or wall motion abnormalities at rest vs. reversible perfusion defects) in the same area. In 20 areas the two methods showed abnormalities in one of the adjacent segments. Two patients had single, distal and moderate stenoses on the left anterior descending artery (which is a usual cause for a negative stress test result) and results of dobutamine stress echocardiography were negative in those cases. There were only nine areas where we could not explain the discordant results of the two methods and coronary angiography had not been performed to validate the result of one of the methods.

Table 2. Disagreement Between Myocardial Ischemia in Patients With No History of Myocardial Infarction

Pt No.	mibi SPECT	Echo	Coronary Angiography
42	Ischemia	Negative	Not done
59	Ischemia	Negative	LAD stenosis
69	Ischemia	Infarction	LAD distal stenosis
76	Ischemia	Infarction	3VD
102	Ischemia	Negative	LAD distal stenosis
12	Negative	Ischemia	Open stent RCA (false positive?)
57	Infarction	Ischemia	Not done

Echo = dobutamine echocardiography; LAD = left anterior descending coronary artery; mibi SPECT = ^{99m}technetium single-photon emission computed tomography; RCA = right coronary artery; 3VD = multiple-vessel disease.

Relation of dobutamine stress test to coronary angiographic findings. Of 105 consecutive patients, 21 met the criteria of no previous myocardial infarction, normal wall motion at rest and a recent coronary angiogram (<3 months). Twelve of these 21 patients had significant coronary artery stenosis (>50% diameter stenosis). Four of these 12 patients had single-vessel disease; in all 4, the stenoses were located on the left anterior descending artery and in 2 they were on the distal portion of this artery. Another three patients had two-vessel disease—two patients with stenoses on the right coronary and left anterior descending artery branches and one patient with left circumflex and left diagonal branch stenoses—and five patients had triple-vessel disease. In the other nine patients, no significant coronary stenosis was detected; four of the nine had a normal coronary angiogram and five had recent balloon angioplasty or atherectomy with no significant coronary abnormality at the time of the catheterization and the dobutamine stress test. The mean age and hemodynamic data of this subgroup were comparable with those of the whole group.

Echocardiography detected 9 and mibi SPECT detected 10 of the 12 patients with significant coronary abnormalities. Both tests had one false positive result (Table 3). Combining the results of echocardiography and mibi SPECT the sensitivity increased (11 of 12), whereas specificity decreased slightly (2 of 9 false positive). Poor agreement was found between ST segment changes during stress testing and the coronary angiographic findings (42%, kappa = 0.077); this

Table 3. Comparison of Dobutamine Echocardiography and mibi SPECT in Patients With Coronary Angiography and Normal Wall Motion at Rest

	CAD + (sensitivity)	CAD − (specificity)
Echo+	9/12 (75%)	1/9 (89%)
SPECT+	10/12 (83%)	1/9 (89%)
Echo+ or SPECT−	11/12 (92%)	2/9 (78%)

CAD+ = patients with angiographically proved coronary artery disease; CAD− = no significant coronary stenosis at the time of cardiac catheterization. Echo+ = new wall motion abnormality during dobutamine stress test; SPECT+ = reversible perfusion defect on ^{99m}-technetium isonitrile (mibi) single-photon emission computed tomography during stress test.

result can be explained in part by the displacement of ECG leads during dobutamine echocardiography. The agreement between the presence of chest pain and angiographic findings was acceptable (71%, kappa = 0.43). The results of echocardiography and mibi SPECT were in agreement in 15 of 21 cases (71%, kappa = 0.43). Three patients with single-vessel disease (all with distal lesions and moderate stenoses) had negative findings on stress echocardiography whereas SPECT did not detect one case of single-vessel disease and one of double-vessel disease.

Discussion

Dobutamine stress testing is increasingly used to elicit myocardial ischemia and detect significant coronary artery disease, mostly in conjunction with echocardiography (5,11). Recently dobutamine stress echocardiography and 201-thallium scintigraphy have been used in different clinical settings, such as the diagnosis of coronary disease, the assessment of the results of coronary angioplasty or risk stratification before vascular surgery (8,14,15). However, it is unclear to what extent the two tests provide concordant information; for obvious financial considerations, stress echocardiography should be favored if it gives the same information as perfusion scintigraphy. The widespread use of perfusion scintigraphy is limited by the high cost of the procedure and the exposure of the patients to radiation. Our primary goal was to establish the potential role of dobutamine stress echocardiography as an alternative to perfusion scintigraphy. To our knowledge, this is the first large scale study in which dobutamine stress echocardiography and perfusion scintigraphy were performed simultaneously. In addition, this is the first study in which 99m-technetium isonitrile (mibi) has been used in conjunction with SPECT imaging during dobutamine stress testing. Our patient group was primarily referred for pharmacologic perfusion scintigraphy to investigate chest pain. Dobutamine (with the addition of atropine, when necessary) induced new or worsened wall motion abnormalities in 38 (37%) of 102 patients, whereas transient perfusion defects were detected in 45 (44%). Chest pain occurred in 35 patients and pathologic ST segment deviation in 28 (ST depression in 21 and ST elevation in 7). The overall agreement between the two methods for the detection of presence or absence of myocardial ischemia was 74%. When the results of both tests were positive, the agreement for the localization of transient defects was good. The concordance was similar to that found by others (17) as well as by our group (1,23) in a comparison of exercise perfusion imaging with immediate postexercise echocardiography. The agreement between echocardiography and SPECT for detection of ischemia was better in patients with normal (84%) than in those with abnormal wall motion at rest. However, in both patient groups, the incidence of a positive SPECT finding was greater than that of a positive echocardiographic finding. This trend was more evident in the group with abnormal wall motion at rest, in which a transient perfusion defect more frequently occurred in the infarcted area without a deterioration of wall motion or wall thickening in the same area. These results are similar to those found in correlative echocardiographic and scintigraphic studies during physical exercise (1,17).

Several mechanisms can be advocated to explain these discrepancies. 1) It is well known that perfusion scintigraphy can detect myocardial malperfusion in addition to true myocardial ischemia leading to a greater number of positive scintigraphic than echocardiographic results. This outcome is consistent with our recent observation that positive results are more frequently found with exercise perfusion scintigraphy, than with exercise echocardiography in patients with moderate coronary stenoses. In contrast, the rate of positivity with both techniques was similar in patients with severe stenoses. In the present study, because patients were primarily referred for scintigraphic study rather than coronary angiography, we did not use coronary angiography as a standard. Instead, we compared the functional consequences of myocardial ischemia detected by the two noninvasive methods. Therefore, the hypothesis of the influence of the severity of coronary artery stenoses on the different tests could not be verified.

2) The higher incidence of a positive SPECT result in the infarcted area, and especially in akinetic areas, requires another explanation. Quinones et al. (17) clearly delineated the possible explanations of this discrepancy when 201-thallium was used as a radiotracer. In our study, we used mibi instead of thallium, because we assumed that it was more suitable for SPECT imaging as a result of its high energy (18) and lack of significant redistribution. The latter property of the radiotracer could overcome the problem of differential regional washout rate, which could be the cause for reversible perfusion defects not directly related to malperfusion or ischemia.

3) Another explanation for the higher incidence of transient perfusion defect in akinetic areas at rest is hibernating myocardium and also the tethering effect of the infarcted area on the noninfarcted myocardium (17). However, the clinical and prognostic significance of areas with fixed echocardiographic defects showing partial redistribution on perfusion scintigraphy is uncertain and deserves further

investigation. In particular, studies have to address the impact of coronary revascularization in these areas.

Study limitations. Some limitations to the present study should be acknowledged. 1) Both regional wall motion and myocardial perfusion were assessed visually. Although we have found a small intra- and interobserver variability in the interpretation of SPECT images, the lack of quantitative analysis could affect the results (25). Quantitative analysis of exercise wall motion assessed by echocardiography has been attempted in normal persons (26). However, a semiquantitative reading of perfusion scintigraphy and echocardiography is the routinely applied method in most clinical laboratories (2–4).

2) Coronary angiography was not used as the reference standard in all patients. However, we do not consider this a major limitation because our goal was to compare the value of two different tests to assess the functional significance of coronary disease. Furthermore, it would not be correct to assess the diagnostic value of the tests in patients in whom the application of coronary angiography was strongly dependant on the test results.

Conclusions. Our study indicates good agreement between echocardiography and mibi SPECT with respects to the response to dobutamine in patients with normal wall motion at rest for the detection myocardial ischemia. More studies are warranted in patients with previous myocardial infarction in whom the concordance was less satisfactory.

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CHAPTER 11.

Prognostic value of dipyridamole MIBI SPECT and dipyridamole stress echocardiography for new cardiac events after an uncomplicated myocardial infarction.

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Submitted.

Summary.

A high-dose dipyridamole stress-test (0.84 mg/kg in 6 min) with simultaneous MIBI SPECT, echocardiographic imaging and 12-lead ECG monitoring was performed in 89 patients before hospital discharge after an uncomplicated myocardial infarction. The aim of this study was to determine the prognostic value of a high-dose dipyridamole stress test for new cardiac events, and to compare the relative values of SPECT, echo and ECG in a postinfarct dipyridamole stress test.

At 2 years post-infarct 9 patients (10%) had died, 5 pts (6%) had suffered a non-fatal reinfarction and 14 pts (16%) had been readmitted for a revascularization procedure. Cardiac death had occurred in 5/48 (10%) of patients with a positive SPECT versus 4/41 (10%) with a negative SPECT (n.s.), in 6/31 (19%) with a positive echo versus 3/56 (5%) with a negative echo ($p=0.05$), and in 5/20 (25%) with a positive ECG versus 4/66 (6%) with a negative ECG ($p=0.01$). Cardiac death and/or reinfarction had occurred in 8/48 (17%) pts with a positive SPECT versus 6/41 (15%) with a negative SPECT (n.s.), in 6/31 (19%) with a positive echo versus 8/56 (14%) with a negative echo (n.s.) and in 5/20 (25%) with ST changes versus 9/69 (14%) without ST changes (n.s.). Thus the predictive value of the dipyridamole stress test for new cardiac events after an uncomplicated infarction was limited, irrespective of the method used to detect ischemia. Reversible perfusion defects were identified more frequently than new wall motion abnormalities or ECG-changes, but did not predict late events. A positive dipyridamole-echo or ECG both were associated with a higher late mortality, but did not predict other cardiac events.

Key words: Dipyridamole stress echo
Dipyridamole MIBI-SPECT

Introduction.

The indication for coronary angiography[1,2] in patients after an uncomplicated myocardial infarction (no signs of heart failure, postinfarct ischemia nor late ventricular arrhythmias) remains controversial. Ideally, non-invasive methods should be reliable for risk stratification and for selecting the patients that need further invasive investigation and therapy. Myocardial ischemia during stress may identify patients at risk, and the value and limitations of post-infarct exercise testing have been documented extensively [3-10]. However, many of these patients are unable to perform an adequate level of exercise, and the sensitivity of electrocardiographic ST-segment changes has limitations.

Pharmacologic stress-testing combined with echocardiography or nuclear imaging are highly reliable techniques for the detection of ischemic heart disease[11-18], but the value of these techniques for risk stratification after an uncomplicated myocardial infarction remains unclear despite previous studies[19-23].

We conducted a prospective study on the prognostic value of dipyridamole stress-tests in patients prior to discharge after an uncomplicated myocardial infarction. A direct comparison was made of echocardiographic, MIBI SPECT and electrocardiographic evidence of ischemia during the test, and the results were related to new events (reinfarction and cardiac death) and the need for revascularization during two years follow-up.

Patients and Methods.

Between October 1989 and January 1991, 89 consecutive patients with a recent uncomplicated myocardial infarction were studied after they were transferred from the coronary care unit to the ward. Infarction diagnosis was based on the combination of typical complaints and ST-segment elevation followed by positive CPK and CPK-MB levels. Patients were excluded from this study if they had late ventricular arrhythmias, signs of heart failure or chest pain after the acute event. The dipyridamole stress-test was performed prior to discharge, after informed consent was obtained. Results of the test were not used for clinical decision making. Routine exercise electrocardiography and coronary angiography were the tests, performed at the request of the attending doctor, on which patient management was based. All medication was continued, including beta-blockers in 60 patients, oral nitrates in 37 and calcium antagonists in 22. No patient used aminophylline-

containing drugs. Tea, coffee and other caffeine-containing beverages were withheld at least 12 hours prior to the test. Dipyridamole was infused into the antecubital vein in a dose of 0.84 mg/kg over a six minute period under continuous electrocardiographic monitoring. We chose a high dose since this increases the sensitivity of echocardiography in our experience and that of others[24]. Aminophylline (200 mg) was administered intravenously 10 minutes after the end of dipyridamole infusion, or earlier if there was evidence of ischemia which did not resolve spontaneously.
Standard 12-lead ECG's were recorded before the start of dipyridamole-infusion and at the end of every minute, until aminophylline had been administered. The ECG's were analysed by a cardiologist unaware of other test results. Ischemia was defined as at least 1 mm ST-segment depression compared to the rest-ECG, at 80 ms after the J-point.
Four standard echocardiographic views (parasternal long- and short axis, apical two- and four chamber) were obtained and recorded before infusion of dipyridamole and the optimal transducer postions were marked on the chest of the patient. A Hewlett Packard Sonos 1000 echo machine with 2.5 and 3.5 mHz transducers was used. Images were recorded continuously on videotape during dipyridamole infusion and for 10 minutes afterwards, until aminophylline had been administered. They were analysed off-line by two experienced echo-investigators who were unaware of other patient-data, in accordance with methods described before[25]. Briefly, two investigators independently scored 14 segments of the left ventricular wall on a 4 point scale; 1=normal, 2=hypokinetic, 3=akinetic, 4=dyskinetic. An increase in score in one or more segments compared to the wall motion score at rest constituted a positive test. When there was disagreement a third investigator scored the images and a majority decision was attained. Infarct extent was calculated as the number of segments with a rest score >1 and infarct severity as (sum of segmental scores at rest/ number of segments visualized).
The 14 segments were regrouped into six regions of myocardium (anterior septum, posterior septum, posterior, lateral and anterior wall, apex) for comparison between the dipyridamole stress echo and SPECT data.
Technetium-99 m MIBI (370 MBq) was injected intravenously two minutes after dipyridamole infusion had ended, eight minutes before it was antagonized with aminophylline. Stress SPECT images were acquired one hour after dipyridamole and rest-images after 24 hours. This was done using a Siemens Orbiter gamma camera, leap collimator, and a zoom factor (square root 2), 15% energy window and 64x64 word mode matrix. Thirty-two projections were taken over 180 degrees starting at the 40 degree left posterior oblique position. Acquisition time per projection was 45 seconds.

After median prefiltering of the acquired data, images were reconstructed using a filtered back projection algorithm with a ramp reconstruction filter. The images were analysed in accordance with methods described previously[25]. Briefly, a total of 47 segments were assigned a score on a scale of five grades. A positive dipyridamole stress SPECT result was defined as one with an improvement from stress to rest by at least one grade in at least two contiguous segments.
The extent of the infarction was calculated as the number of segments with a rest score >2 and the severity of the infarction was calculated as the sum of the segmental scores at rest.
The 47 segments were regrouped into 6 regions of myocardium (anterior septum, posterior septum, posterior, lateral, anterior wall, apex) for comparison with the echocardiographic findings.
Symptom limited exercise ergometry was performed in 66 of these 89 patients, and coronary angiography in 58. These studies were performed, as mentioned above, for clinical decision-making at the request of the attending doctor. Patients with gross obesity, orthopaedic or neurological disabilities or exercise-limiting peripheral vascular or pulmonary disease were excluded from exercise stress testing. Upright bicycle ergometry, starting at 40 Watts and increasing by 20 Watts per minute, was performed. Antianginal therapy was continued. ST depression of at least 1 mm at 80 msec after the J-point was considered significant for ischemia and the test was stopped for significant chest pain, dyspnea, fatigue, ventricular arrhythmias, fall in systolic blood pressure by 20 mmHg from baseline or >2 mm ST depression 80 ms after the J point.

Follow-up data were collected at two years post infarct. The data were obtained from the outpatient clinic visits and completed when necessary by contacting the patient's general practitioner. Endpoints were 1) cardiac death, 2) nonfatal reinfarction and 3) coronary angioplasty or bypass surgery. Kaplan-Meyer curves for survival and infarct-free survival were constructed and compared by log rank tests (Mantel-Cox).

Results.

Of the 89 patients, 70 were male and 19 female. Mean age was 60 (±11) years and 27 had a history of a previous infarction. The site of infarction was inferior/posterior in 48 patients, septal/ anterior/anterolateral in 34, lateral in 3, and in 4 the site was undetermined. Thirty-one had had thrombolytic

therapy. Thirty had a non-Q wave infarction (with a maximal CPK level of 463 ±338 U/l), 59 had developed a Q wave (CPK's 1189 ±1074) on the rest ECG at the time of the stress-test.
The dipyridamole stress test was performed 9 (±5) days after the infarction and was completed in all patients without complications. Heart rate increased from 70 ±14 to 85 ±14, ($p<0.0001$) and systolic blood pressure decreased from 125 ±16 to 121 ±21 ($p<0.01$) during dipyridamole-infusion. Twenty-four patients developed chest pain during the test.
ST depression > 1 mm occurred in 20 of 86 patients. ST segments were not assessed in 3 patients because of left bundle branch block.

Dipyridamole stress echocardiography

In 87 of the 89 patients the images were of adequate quality for analysis; 63 (72%) had wall motion abnormalities at rest. Dipyridamole-induced new wall motion abnormalities developed in 31 (36%). In 21 patients the new abnormality developed in areas adjacent to those with a resting wall motion abnormality (regarded as the infarct zone), in 7 patients the new abnormalities were in areas with normal resting wall motion (regarded as remote from the infarct zone) and 3 patients had new wall motion abnormalities in both the infarct zone and remotely.

Dipyridamole SPECT

Fixed perfusion defects were seen in 78 of the 89 patients (88%) and reversible defects occurred in 48 (54%). Of these 48, 29 occurred in areas with perfusion defects at rest (regarded as the infarct zone), 7 occurred in areas with normal rest perfusion (regarded as the remote zone) and in 12 patients there were reversible defects both in the infarct zone and remotely.

Relationship between dipyridamole test results.

The frequency of reversible defects on SPECT (54%) was greater than the frequency of either new wall motion abnormalities on echocardiography (36%), chest pain (27%) or ST-segment depression on ECG (23%). Figure 1 shows the agreement between the different imaging methods for ischemia during dipyridamole infusion. Concordance was 61% between SPECT and echo (kappa-value =0.236), 50% between SPECT and ECG ($k=0.024$) and 70% between echo and ECG ($k=0.290$).

Exercise electrocardiography

Bicycle ergometry was performed in 66 patients before hospital discharge. They achieved a significant increase in heart rate from 71($\pm$13) to 126($\pm$22) ($p < 10^{-6}$) and systolic blood pressure rose from 127($\pm$17) to 169($\pm$32) mmHg from rest to peak stress ($p < 10^{-6}$). Significant ST depression occurred in 33 patients (50%), chest pain in 13 and dyspnoea in 23. Nine patients achieved a work load less than 100 W. The concordances for exercise-induced ST depression and dipyridamole- test results are illustrated in figure 2. Concordance between exercise-ECG and dipyridamole-ECG was 55% (kappa-value =0.150), between exercise-ECG and dipyridamole echo concordance was 55% (k=0.112), and between exercise-ECG and dipyridamole-SPECT it was 56% (k=0.121).

Follow-up results.

Follow-up was complete at 2 years postinfarct in 88 patients, and up to 16 months in one. Nine patients had died; one from right heart failure (inferior infarction, cor pulmonale secondary to emphysema), one from a ruptured aortic aneurysm, three died in the hospital following a reinfarction and four had a sudden death at home, most probably of cardiac origin. Five patients had suffered another non-fatal myocardial infarction and from those who had various degrees of recurrent angina, fourteen had undergone a revascularization procedure.

Relationship between dipyridamole stress tests and new cardiac events

The main results are summarized in tables I and II and in figures 3 and 4.
Five out of 48 patients with a positive SPECT had died versus 4/41 with a negative SPECT, 6/31 with a positive dipyridamole stress echo versus 3/56 with a negative echo and 5/20 with ST-depression during the dipyridamole test versus 4/66 without ST changes. Reinfarction and/or death occurred in 8/48 patients with a positive dipyridamole-MIBI SPECT versus 6/41 with a negative SPECT, in 6/31 patients with a positive dipyridamole-echo versus 8/56 with a negative echo and in 5/20 with ST-segment depression versus 9/66 without ST-changes (Table I).
When a log ranksumtest is applied to the Kaplan-Meyer curves (figures 3 and 4), only the survival curves for echo and ECG data are different. However,

the numbers of events in these curves is limited, and the overlap in the 95% confidence intervals (Table 1) is considerable.
The results of pre-discharge examinations in the patients who had a cardiac event during the follow-up are summarized in table II. Among these 14 patients, there were 3 in whom the dipyridamole stress test was negative by all methods. Also the angiographic findings in these patients were diverse and not different from the whole subgroup that had been catheterized (25 patients with single-vessel disease, 18 two-vessel disease, 15 three-vessel disease; 20 patients with 100% stenosis of the infarct related vessel, 6 with 90-99% stenosis, 26 with 50-90%, 5 with less than 50% stenosis, unknown in one).
Infarct extent and severity in the resting images did not predict subsequent mortality. MIBI SPECT score of infarction extent (number of segments) was 9.0 (±6.7) for the survivors versus 14.7 (±10.5) for those who died ($p=0.06$), and the score for infarction severity (sum of segment scores) was 23.9 (±20.4) for the survivors versus 37.0 (±30.5) for those who died ($p=0.15$). The echocardiographic score for infarction extent was 3.76 (±3.22) for the survivors versus 3.40 (±2.79) for those who died ($p=0.81$), and the score for infarction severity 1.34 (±0.33) for survivors and 1.36 (±0.29) for those that died ($p=0.93$).

Relationship between exercise electrocardiography and events at follow-up

Six out of 23 patients who were excluded from an exercise test died during follow-up, versus 3/66 ($p=0.01$, Fisher exact) who had been exercised prior to discharge (Table III). More patients with a positive than a negative exercise test had subsequently angiography and revascularization, but it should be realized that results of the exercise test were available to the attending doctor and used for decision making, this in contrast to the results of the dipyridamole tests. Just like the dipyridamole- echo and ECG, the exercise-ECG did not predict recurrent myocardial infarctions (Tables I and III).

Discussion.

In the present study, a direct comparison between dipyridamole stress echo and MIBI SPECT imaging was performed in a group of consecutive patients with a recent uncomplicated myocardial infarction. The aim of the study was twofold, 1) to assess the agreement between dipyridamole stress echo, MIBI-

SPECT and ECG for the diagnosis of residual ischemia and 2) to compare the prognostic value of these modalities, relative to the generally accepted conventional exercise ergometry. As far as we are aware of, this is the first study which addresses these questions in patients with a recent and uncomplicated myocardial infarction.

Dipyridamole MIBI SPECT yielded the highest incidence (54%) of an ischemic response, while dipyridamole stress echocardiography was positive in 36% of the patients. ST-segment depression was the least frequent marker of dipyridamole-induced ischemia (23%). Due to the different distribution of the detection of ischemia with the different methods, the agreement between them was poor, ranging from 50% (between SPECT and ECG) to 70% (between echo and ECG). There are different reasons to explain the discrepancy between the different markers of ischemia. Firstly, it is known from the "ischemic cascade" that the perfusion heterogeneity is the first phenomenon during stress, followed by a wall motion abnormality. ST-segment changes are the last phenomenon during stress induced ischemia. Therefore, if the vasodilation is submaximal, it is not surprising that reversible perfusion defects can be seen in the absence of echo and/or ECG changes, indicating maldistribution of flow rather than true ischemia. Secondly, it is intriguing that agreement between the tests is much worse in this postinfarct population than in a non-infarct population[25]. The presence of resting wall motion abnormalities and fixed perfusion defects in postinfarct patients may degrade the reliability of either test. A third factor which may contribute to the higher frequency of perfusion defects than mechanical markers of ischemia, is the use of antianginal medication, which was not discontinued in our patients. Recent data indicate that the sensitivity of dipyridamole stress echocardiography for the detection of coronary artery disease is reduced by some 30% in patients using anti-anginal therapy[26]. The effect of anti-anginal medication on the sensitivity of dipyridamole-SPECT is unclear. Some have reported that beta-blockade does not affect dipyridamole thallium scintigraphic images[27], whereas others have reported that beta-blockers increase and calcium antagonists decrease SPECT defect size[28,29].

The prognostic information that we obtained from the dipyridamole stress tests were disappointing, even if both positive dipyridamole echo- and electrocardiography tests were associated with higher late mortality. If the number of patients had been much larger, and thus confidence intervals smaller, statistical significance might become stronger. However, since our goal is to find a test that helps to predict the fate of the individual patient, a test of which the predictive value, if any, can be demonstrated only in very large series has limited value in clinical practice. Furthermore, the observation in this study that all five nonfatal reinfarctions occurred in patients with both negative dipyridamole echo and ECG adds more doubt to the clinical value of this test in this selected population. When a non-fatal reinfarction was added as an end-point to cardiac mortality, all 3 ischemic markers lost even any tendency of prognostic usefulness. This is consistent with previous data showing how difficult it is to predict a reinfarction in asymptomatic postinfarct patients[6-10,23].

The number of events and the predictive value of either test might have been much higher if recurrent angina had been considered an endpoint. Several recent studies have demonstrated that evidence of ischemia during an exercise test predicts recurrent angina but not reinfarction or cardiac death[9,30]. However, we did not include recurrent angina as an endpoint for two reasons; first, uniform and reliable assessment of new or recurrent angina is difficult, especially if patients are seen by many different doctors. Second, prediction of chest pain is not a goal for a test; the patient can tell when he has recurrent chest pain, and it has no therapeutic consequences until then.

Interestingly, the extent and severity of wall motion abnormalities and of perfusion defects at rest were not predictive of late mortality (although this might be different with a longer follow-up). This is very likely due to the selection criteria, by which patients with advanced left ventricular dysfunction were excluded, and indeed no mortality from left ventricular failure occurred during follow-up.

Our negative results regarding the prognostic value of MIBI SPECT are in contrast to previous thallium scintgraphic studies[19-21,31,32]. It is unlikely that this results from the use of 99m Technetium rather than thallium, or the use of SPECT rather than planar scintigraphy. Most positive studies included patients with LV dysfunction, used recurrent angina as an endpoint, or both. The selection of patients and endpoints in our study may be the main cause of the different results.

Symptom-limited bicycle ergometry was performed in 66 patients. Similar to previous studies[7,33], patients with a negative test who performed 100 Watts or more had an excellent survival (the single patient who died after a "negative" exercise test had been able to perform only 80 W). All mortality occurred in patients with either a positive exercise test, a low exercise tolerance or patients unable to perform the exercise test. However, when it comes to predicting new myocardial infarctions, the value of the exercise test was, in this experience, as limited as the value of any dipyridamole stress-test. This is in accordance with other studies reporting the limitations of a postinfarct exercise test to predict reinfarctions[8,30].

Would these patients be better off if they all underwent coronary angiography

? A review of the available angiographic data showed that our population was diverse in extent and severity of coronary disease, but the subset of patients who suffered an event during follow-up did not constitute a uniform group of more severe angiographic abnormalities. Our data do not allow firm conclusions on the predictive value of angiography in this low-risk population. However, larger studies have also reported that clinically low-risk post infarct patients do not benefit from angiography[33-35].

Limitations of the study.

The number of hard events during follow-up was limited. This was to be expected, since we selected patients who are at "low risk" by all clinical predictors. The number of events and the prognostic value of the test might have been higher if we had included patients with additional risk factors, such as postinfarct angina. However, these patients already have an indication for invasive investigation. Our study population represents the one in which pharmacological stress-testing might have its main role for post infarct risk-stratification; namely those who do not have an a priori indication for cardiac catheterization and angiography. The limited number of events resulted in wide confidence intervals.
Another limitation of the study may be the continuation of anti-anginal medication during the test. As mentioned above, it is unknown to what extent the potential effects of anti-anginal medication on cardiac imaging tests influence the prognostic utility of these tests.

Relationship to other studies.

Since the start of this study, in October 1989, some reports have been published on the predictive value of dipyridamole stress tests after a myocardial infarction.
Bolognese et al.[14] performed a dipyridamole stress echo (no SPECT) in 217 patients after a first uncomplicated myocardial infarction. At a mean follow up of two years, 4 out of 128 patients with a positive test had died versus 1 out of 89 with a negative test, and 6 out of 128 with a positive test had a nonfatal reinfarction, versus 1 out of 89 with a negative test. Thus this study provides stronger evidence than our study that a positive dipyridamole stress test after infarction is associated with a higher mortality, and it also provides evidence, in contrast to our study, that a positive test is associated with a higher reinfarction rate. Nevertheless, the predictive value of a positive test

is extremely low, limiting the usefulness for clinical decision making.
Sclavo et al.[23] performed a dipyridamole stress echo in 107 asymptomatic patients 5 to 8 days after an uncomplicated myocardial infarction treated with thrombolysis. Although again the limited number of events precludes firm conclusions, they found, more in agreement with our study, that the incidence of cardiac events was not predicted by the dipyridamole stress echo results.
The EPIC study, of which preliminary results were presented at the meeting of the American College of Cardiology[36], had a 2-year mortality of 9.4% in patients with a positive dypiridamole stress echo (compared to 19% in our patients) versus 3% (5% in our patients) in those with a negative test. No ECG or scintigraphy was part of in this study. The results of this multicenter study will have a greater statistical power than our study. However, as mentioned above, if a test has a limited predictive value in small series, its value for decision making in the individual patient is limited, even when statistical significance is reached in larger series.
In summary, some indications for invasive diagnosis and therapy post infarct are well defined[1,2]. In patients with an uncomplicated infarction (no evidence of heart failure, residual ischemia or late ventricular arrhythmias) a negative exercise test at an adequate level of stress is associated with a low mortality, in many previous studies as well as in this study, but has limitations when it comes to predicting new infarctions. This study cannot provide evidence that dipyridamole is superior to exercise as the modality of choice for postinfarct stress tests. Dipyridamole echocardiography can be considered in patients unable to perform an exercise test, in those with a poor exercise tolerance or with equivocal exercise results. The test is safe early post infarct, but its role and clinical value in postinfarct risk stratification remains questionable. In our experience the value of a dipyridamole stress test to predict new cardiac events after an uncomplicated myocardial infarction was limited, irrespective of the method used to detect ischemia, MIBI SPECT being the least discriminative.

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1a

		SPECT +	SPECT -	
ECHO	+	22	9	31
	-	25	31	56
		47	40	

concordance = 61%

1b

		SPECT +	SPECT -	
ST↓	+	11	9	20
	-	34	32	66
		45	41	

concordance = 50%

1c

		ECHO +	ECHO -	
ST↓	+	12	8	20
	-	17	47	64
		29	55	

concordance = 70%

Figure 1.

1a: Concordance for ischemia between dipyridamole SPECT (transient perfusion defects) and stress echocardiography (new wall motion abnormalities).

1b: Concordance for ischemia between dipyridamole SPECT and ECG (ST-depression).

1c: Concordance for ischemia between dipyridamole echocardiography and ECG.

2a

Dip-ECG \ X-ECG	+	-	
+	10	5	15
-	22	26	48
	32	31	

concordance = 55%

2b

SPECT \ X-ECG	+	-	
+	19	15	34
-	14	18	32
	33	33	

concordance = 56%

2c

ECHO \ X-ECG	+	-	
+	13	9	22
-	20	23	43
	33	32	

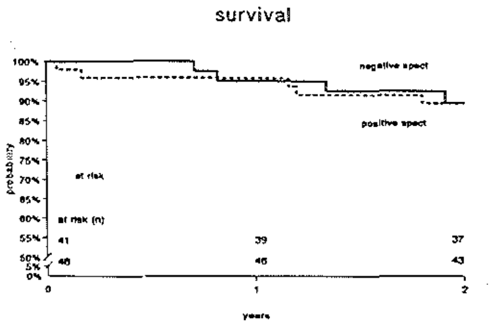
concordance = 55%

Figure 2:

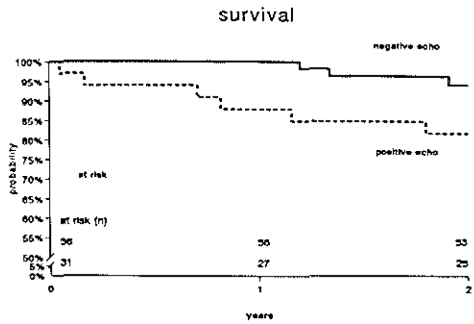
2a: Concordance for exercise induced ST-depression and dipyridamole induced ST-depression.

2b: Concordance for exercise-induced ST- depression and dipyridamole induced reversible perfusion defects on SPECT.

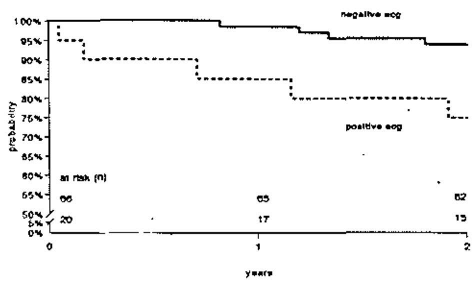
2c: Concordance for exercise-induced ST-depression and dipyridamole induced new regional wall motion abnormalities on echo.



3a



3b



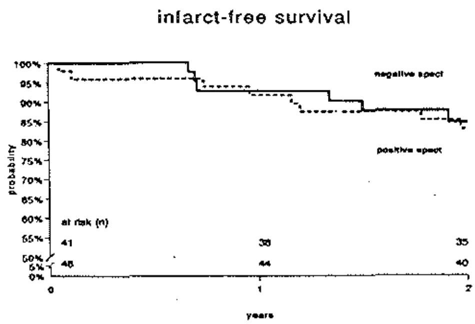
3c

Figure 3.

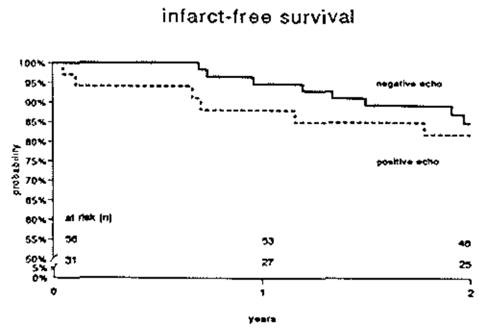
3a: Survival of patients with a positive dipyridamole SPECT versus those with a negative dipyridamole SPECT before discharge after an uncomplicated myocardial infarction; p=NS.

3b: Survival after positive versus negative dipyridamole-echo; p=0.05

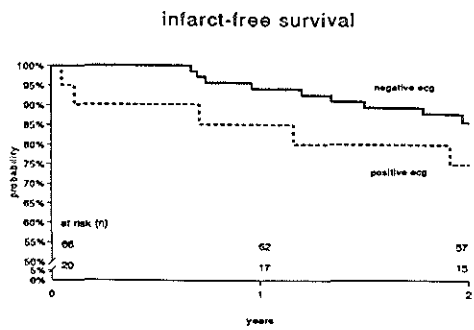
3c: Survival after positive versus negative dipyridamole-ECG; p=0.01
Although the survival curves for echo and ECG are significantly different in a log ranksum test, this test should be interpreted with reservation because of the limited number of deaths. Actually two patients, who died early after a positive test by all methods, are largely responsible for the differences.



4a



4b



4c

Figure 4.

4a: Infarct-free survival of patients with a positive dipyridamole SPECT versus those with a negative dipyridamole SPECT before discharge after an uncomplicated myocardial infarction.

4b: Infarct-free survival after positive versus negative dipyridamole-echo.

4c: Infarct-free survival after positive versus negative dipyridamole-ECG. None of these curves are significantly different (log ranksum test).

Table I. Numbers of patients with a positive versus negative dipyridamole stress SPECT, echo and ECG and the numbers and percentages of patients from these subgroups that had suffered cardiac death, reinfarction or a revascularization procedure within two years post-infarct

	Death	Infarct	Revasc	Mortality	Death/re-MI
SPECT pos.(n=48)	5	3	7	10% (3-22)	17% (8-31)
SPECT neg.(n=41)	4	2	7	10% (3-23)	15% (6-30)
Echo pos.(n=31)	6	0	5	19% (7-37)	19% (7-37)
Echo neg.(n=56)	3	5	9	5% (1-15)	14% (8-27)
ECG pos.(n=20)	5	0	2	25% (8-48)	25% (8-48)
ECG neg.(n=66)	4	5	12	6% (2-15)	14% (7-25)

Table II. Results of the dipyridamole-stress test (reversible perfusion defects on SPECT, new regional wall motion abnormalities on Echo, ST and angina) before discharge and results of coronary angiography in the patients who suffered cardiac death or nonfatal reinfarction within 24 months. "No.Ves" is number of vessels diseased on coronary angiography, IRV is stenosis in the presumably infarct-related vessel. I and R (in the SPECT and Echo-tables) is Infarct-region and Remote.

Cardiac death

pt nr.	months from infarct	CPK	rest ECG	SPECT	ECHO	ST	Angina	No.Ves	IRV
3	15	522	Q	I	-	-	-	1	100%
4	3	1800	Q	-	-	+	+	1	50-90%
10	9	460	Q	-	I+R	+	+	1	100%
15	1	1100	Q	I+R	I	+	+	3	100%
16	14	608	n-Q	I+R	I+R	+	+	1	50-90%
30	10	476	Q	-	I	-	-		
52	14	400	Q	-	-	-	-	3	50-90%
57	2		Q	I	R	-	-	3	100%
62	22	1155	Q	I	I+R	-	-		

Nonfatal reinfarction.

pat nr.	months from infarct	CPK	rest ECG	SPECT	ECHO	ST	Angina	No.Ves	IRV
25	18		Q	-	-	-	-		
26	23	381	n-Q	I	-	+	-	1	50-90%
32	11	423	Q	R	-	-	-	1	50-90%
42	9	1215	Q	I+R	-	-	-		
46	8	528	n-Q	-	-	-	-	2	50-90%

Table III. Exercise electrocardiography versus new cardiac events during follow-up.

	Death	Infarct	Revasc.
	n=	n=	n=
X-ECG pos. (n=33)	2	0	6
X-ECG neg. (n=33)	1	4	3
no X-ECG (n=23)	6	1	5

PART FOUR

CONCLUSIONS

CHAPTER 12.

GENERAL DISCUSSION

1) Feasibility and safety of stress echocardiography

The results of the studies reported in this thesis show that stress echocardiography is a feasible technique, both in conjunction with exercise and with pharmacological agents. In our series including about 500 patients, only 9 have been excluded from analysis because of poor image quality. Clearly, this is due to the improved resolution of the new echocardiographic devices and the application of digital techniques. However, our results indicate that the impact of digital techniques on exercise echocardiography is more significant than on pharmacological stress echocardiography of which dobutamine has gained a prominent role.

The safety of exercise echocardiography has been documented in large series of patients undergoing exercise electrocardiography and is primarily dependent on the selection of patients. Both our studies and those of other investigators (1) have indicated that pharmacological stress testing is equally safe. Mild side effects occur in about 15% of the patients tested, while severe side effects requiring the interruption of the test are very rare and less than 1%. Stress-induced wall motion abnormalities, which are not a side effect but the end-point of the test, always promptly reversed, either spontaneously after the infusion was stopped, or after administration of an antidote in combination with nitrates. Interruption of the test at the moment the first new wall motion abnormality occurs makes the test safe to perform, but has probably limited the study of its potential role in the diagnosis of multivessel disease.

2) Diagnosis of coronary artery disease and myocardial ischaemia

Myocardial ischaemia is generally due to significant coronary artery stenosis. Baseline regional wall motion abnormalities often indicate the presence of significant stenosis in the related artery. Thus, in these regions diagnosis of coronary artery disease can be made by echocardiography at rest, while stress echocardiography can offer information on the presence of ischaemia. In this case, coronary arteriography can not be regarded as the reference method. In segments dyssynergic at rest the presence of stress-induced wall motion abnormalities should be better compared with another imaging test, such as nuclear perfusion imaging.

The diagnostic accuracy of stress echocardiography in detecting coronary artery disease has been reported by several groups (2-29). In Table I, II, and III the results of stress echocardiography (exercise, dobutamine, dipyridamole) limited to patients with normal wall motion at rest and/or no previous myocardial infarction are reported. Thus, the confounding effects of the presence of wall motion abnormalities at rest should be avoided. Overall sensitivities ranged from 48% to 97% and specificities from 64% to 100%. These differences can be explained by patient selection, proportion of patients on medication, protocols of stress and criteria for the definition of coronary artery disease. In Table IV, these issues on dobutamine stress echocardiography are presented. Interestingly, the cumulative values of the different tests are similar, and independent of the type of stress employed. Sensitivities are 81%, 80% and 71%; specificities are 87%, 88% and 94%, for exercise, dobutamine and dipyridamole, respectively. Moreover, in this selected population the results of stress echocardiography compare favorably with those obtained with exercise electrocardiography (Table V).

The comparison between stress electrocardiography and stress echocardiography has different implications according to the different subgroups of patients. Patients with rest S-T segment abnormalities due to left ventricular hypertrophy, left bundle branch block, digitalis therapy or sometimes prior myocardial infarction have an uninterpretable exercise test. Furthermore, some patients referred for stress testing are either unable to exercise or exercise submaximally. In these clinical situations, the primary use of stress echocardiography should be recommended. Both sensitivity and specificity for the diagnosis of coronary artery disease are higher with stress echocardiography, a method which also offers the unique advantage of locating the site, the extent, and the severity of myocardial ischaemia.

3) Comparison with nuclear techniques

Myocardial perfusion scintigraphy is the most widely applied imaging technique for the evaluation of patients with coronary artery disease. Exercise thallium scintigraphy has been utilized in patients with stable angina and uncomplicated myocardial infarction, both for diagnostic and prognostic purposes (30-33). However, myocardial scintigraphy has some disadvantages. First, the specificity of the test in unselected population is suboptimal. Second, it requires sophisticated and expensive techniques, not available in every diagnostic center. Third, radiation exposure becomes a limitation when serial studies are needed. Finally, the cost of a test is relatively high and represents a favorable factor for echocardiography in terms of cost/effectiveness ratio. Based on individual studies, stress echocardiography and nuclear imaging (radionuclide ventriculography, myocardial perfusion scintigraphy) have comparable degrees of sensitivity and specificity for the detection of coronary artery disease (Table VI). Echocardiography is now widespread available, not limited to few centers, and its versatility offers the unique advantage to obtain information from the patient in real-time, quickly, at low-cost, and in many different clinical situations. Furthermore, stress echocardiography is not limited to a few experts, although the technique is operator-dependent. Indeed, the test can be reliably interpreted by every cardiologist after adequate training and some experience (37).

In this thesis, a comparison between stress echocardiography and myocardial perfusion scintigraphy has been done, both with exercise (Part Two, Chapters 2-6) and pharmacological stress (Part Three, Chapter 10 and 11). In all these studies, SPECT revealed the presence of myocardial ischaemia in more patients than stress echocardiography. The reasons of these discrepancies have been discussed in Chapter 7. We feel that all the theoretical mechanisms proposed (small areas of ischaemia with a rapid recovery, suboptimal echocardiographic views of some myocardial regions, wall motion abnormalities at rest, maldistribution of coronary blood flow before ischaemia develops) play an important but not uniformly equal role in many different clinical settings. Interestingly, the agreement between echocardiography and SPECT is similar both with exercise and dobutamine (agreement for ischaemia 77% for exercise and 74% for dobutamine), with a higher prevalence of transient perfusion defects without new wall motion abnormalities in the comparative studies. The slightly lower concordance (61%) and the higher prevalence of ischaemia at SPECT found with dipyridamole as a stress agent (Chapter 11) can be explained with the different mechanism of action of dipyridamole. The vasodilating effect of dipyridamole causes an imbalance of coronary blood flow in the presence of coronary artery stenosis, with a "relative" reduction of flow in the affected area (38). Thus, the prevalence of malperfused myocardial areas without ischaemia is theoretically higher when a vasodilating agent like dipyridamole is used, rather than with exercise or "exercise simulation" with drugs.

4) Comparison between different stress modalities

There are very few data on direct comparison between the different pharmacological stress agents presently used (19,25,39,40). In Chapter 9, we compared the results of dobutamine and dipyridamole stress echocardiography in the same group of patients. We found no statistically significant differences between the two drugs for the diagnosis of myocardial ischaemia, with a concordant diagnosis in 693 out of a total of 736 segments evaluated.

A direct comparison between studies with different selection criteria and different reference methods is difficult. In addition, the influence of antianginal therapy on the tests must be taken into account. Betablockers have a pronounced effect on dobutamine, and recent data indicate that also dipyridamole test is influenced by antianginal drugs (41). When these differences are kept in mind, the results reported in Chapter 9 are similar to those reported by Previtali et al (19).

5) The prognostic value of stress echocardiography

The potential role of stress echocardiography as a test for prognostication in patients after an uncomplicated acute myocardial infarction has been studied and is reported in Chapter 11. In these low-risk patients, the predictive value of a positive test was low, and this limits the usefulness of the test for clinical decision making. However, exercise electrocardiography suffered the same limitations. Since these patients have a low risk anyway, the simple finding of a blood pressure increase of 30 mmHg or more could be considered a sufficient predictor of a good prognosis (42). Thus, the best modality of stress for risk stratification in post-infarct patients remains to be defined in larger series.

WHICH IS THE IDEAL STRESS MODALITY IN COMBINATION WITH ECHOCARDIOGRAPHY?

The practical choice of which type of stress should be coupled with echocardiography needs some general considerations.

1) Dynamic exercise remains the most commonly used provocative test of myocardial ischaemia.
2) Some relevant clinical information obtained during exercise test, e.g. work load, can not be derived from other types of stress.
3) Pharmacological stress is the ideal combination with echocardiography both for practical and technical reasons.

However, the conclusion from all the published data is that stress echocardiography is an useful technique for the evaluation of coronary artery disease, whatever stress modality is applied. Thus, every cardiological center should become familiar with stress echocardiography. Ideally, every echocardiographic laboratory should familiarise themself with more than one stress modality (possibly a vasodilator and an inotropic agent), in order to have a flexible approach to individual patients, although the type of stress used seems less important than being able to perform stress echocardiography.

LIMITATIONS OF THE STUDIES

Stress echocardiography gains increasing popularity and wide acceptance among the cardiology community. Although the results reported in this thesis are positive in general, some limitations of the technique must be addressed.

1) Failure to achieve adequate levels of exercise affects the sensitivity of exercise echocardiography (13). The data presented in Chapter 3 indicate that 8 out of 14 patients with a false negative exercise echocardiographic test did not achieve at least 85% of their age-predicted maximal heart rate. Thus, the accuracy of exercise echocardiography is clearly affected by the prevalence of submaximal heart rate response to exercise. It should be noted that exercise electrocardiography and stress thallium imaging are also dependent on the level of exercise attained (43,44).
2) Exercise electrocardiography is the routine method for functional evaluation of coronary artery disease. The addition of echocardiographic monitoring to standard exercise electrocardiographic stress testing improves both the sensitivity and the specificity of the test for the diagnosis of myocardial ischaemia (71% vs 55%, $p<0.05$; 96% vs 81%, $p<0.05$, respectively, Chapter 3).

   The comparison of exercise electrocardiography with exercise echocardiography in this study was based on the evaluation of ST segment depression on the 12-lead electrocardiogram. To avoid interferences with the echocardiographic transducer, electrocardiographic precordial electrodes were slightly different from standard lead position. The possibility of an adverse effect of such a repositioning the electrocardiographic leads on the accuracy of exercise electrocardiography has not been studied. Theoretically, this suboptimal methodology could reduce the sensitivity of exercise electrocardiography. As far as we know, there are few data in which this confounding issue has been evaluated (45). Irrespective of these potential limitations, our findings are in agreement with data of previous studies (7,8,29).

The same methodological problems could also affect the electrocardiographic response to pl ırmacological stress testing in which a low sensitivity of an ischaemic response has been found (22,24,28). It is unlikely, however, that one or two centimeters of differences in a few precordial leads are responsible for the poor diagnostic value of pharmacological electrocardiographic stress testing.

3) The major limitation of stress echocardiography is the subjective evaluation of the test results. All the studies on stress echocardiography are reported from centers with a recognized reputation on ultrasound imaging. It is not proven that the same positive results will be obtained in centers with less experience. Obviously, stress echocardiography should not be confined to a few excellent laboratories. To obtain widespread acceptance of what is becoming the "first-choice" method for the diagnosis of myocardial ischaemia in the 90's, the criteria for the interpretation of the test should be standardized and objective. However, visual assessment of left ventricular wall motion is often a matter of argument, expecially for minor degrees of dyssynergy. Training in analysis of stress echocardiography is clearly important, and it has been demonstrated that a definite learning curve is necessary to reach adequate reliability in the interpretation of the test (37). An alternative approach of quantitative wall motion analysis is warrented (46,47). The quantitation of regional function involves tracing of endocardial contours, and is dependent on optimal endocardial visualization. This is limited in the apical views, due to the parallel orientation of the ultrasounds with the endocardium. Another problem is related to the temporal heterogeneity among different myocardial regions of the normal left ventricle and to the delayed contraction of some segments during ischaemia (48). Both these factors imply a cumbersome and time-

consuming analysis of several frames of the cardiac cycle, making the quantitative approach unattractive for clinical practice. The development of an easy-to-perform quantitative method for left ventricular wall motion analysis remains the major challenge for stress echocardiography in the next decade.

Colorized wall motion analysis has been proposed to improve the diagnostic quality of a stress echocardiogram (49). The ventricular wall at end-diastole is colorized in blue and serves as reference for the superimposed systolic frames depicted in red. Thus, a red rim along the blue diastolic frame indicates segments which move. This could facilitate segmental left ventricular wall motion analysis.

4) Data reported in Chapter 5 are derived from the study in Chapter 4 and the conclusions are not independent. A small part (<10%) of the patient groups of the studies in Chapter 4 and 6 are also included in the study in Chapter 2, but since this number is very low the final results and conclusions will be not affected.

5) Finally, although patients of these studies are consecutive patients who met the inclusion criteria, coronary arteriography was not performed in a prospective way, thus a possible referral bias should be taken into account as well.

CONCLUSIONS

The early over-enthusiastic period of stress echocardiography is now being replaced by a more realism and consciousness of the problems which are defined with increasing experience. Not all definitive answers are given yet to the questions when and in whom to perform a stress echocardiogram. The results reported in this thesis indicate indeed that stress echocardiography is useful for the diagnosis of coronary artery disease and myocardial ischaemia. The evaluation of revascularization procedures, the role in the prognostication of post myocardial infarction patients, the utility in stratification of patients before non cardiac surgery, and the identification of viable myocardium are only the most attractive aspects of the development of stress echocardiography in the coming years.

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TABLE I.

DIAGNOSTIC VALUE OF EXERCISE ECHOCARDIOGRAPHY IN PATIENTS WITH SUSPECTED CORONARY ARTERY DISEASE

STUDY	REF	Nr	MED	ANGIO	NrCAD	1-VD	SENS	SPEC
Morganroth	2	32	Yes	Visual	21	4	48	91
Maurer	3	36	Yes	Visual	23	6	83	92
Limacher	4	40	Yes	Visual	24	7	79	94
Visser	5	33	?	Visual	20	?	70	92
Iliceto	6	35	No	Visual	16	8	56	95
Armstrong	7	73	No	QCA	51	22	78	86
Ryan	8	64	Yes	Visual	40	25	78	100
Sawada	9	57	Yes	Visual	28	17	78	86
Sheikh	10	34	Yes	QCA	21	21	81	92
Pozzoli	11	75	Yes	Visual	49	33	71	96
Galanti	12	53	No	Visual	27	14	93	96
Crouse	13	228	Yes	Visual	175	66	97	64
Quinones	14	112	Yes	?	86	41	74	88
Marwick	15	95	Yes	Visual	59	34	69	89
Hecht	16	143	Yes	Visual	100	?	91	86
Total		1110			740	298	81	87

Nr = number of patients; MED = antianginal therapy; NrCAD = number of patients with coronary artery disease; 1-VD = number of patients with single-vessel disease; QCA = quantitative analysis of coronary arteriography.

TABLE II.

DIAGNOSTIC VALUE OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY IN PATIENTS WITH SUSPECTED CORONARY ARTERY DISEASE

STUDY	REF	Nr	MED	ANGIO	NrCAD	1-VD	SENS	SPEC
Sawada	17	55	Yes	QCA	35	21	89	85
Cohen	18	70	No	Visual	51	16	86	95
Previtali	19	35	No	Visual	28	16	68	100
Segar	20	51	?	QCA	30	?	90	86
Mazeika	21	36	No	Visual	23	11	65	100
Salustri	22	38	Yes	QCA/Vis	25	13	60	85
Marcovitz	23	53	Yes	Visual	30	?	87	91
Forster	24	21	Yes	Visual	12	4	75	89
Marwick	25	97	Yes	Visual	59	31	85	82
Total		456			293	102	80	88

Legend as in Table I.

TABLE III.

DIAGNOSTIC VALUE OF DIPYRIDAMOLE STRESS ECHOCARDIOGRAPHY IN PATIENTS WITH SUSPECTED CORONARY ARTERY DISEASE

STUDY	REF	Nr	MED	ANGIO	NrCAD	1-VD	SENS	SPEC
Picano	26	76	No	Visual	55	?	75	100
Masini	27	68	No	Visual	26	?	77	93
Previtali	19	35	No	Visual	28	16	57	100
Salustri	28	34	Yes	QCA/Vis	16	?	75	89
Total		213			125	71	94	

Legend as in Table I.

TABLE IV

COMPARISON OF SELECTION CRITERIA, PROTOCOL OF INFUSION, AND CRITERIA OF A POSITIVE TEST IN THE STUDIES ON DOBUTAMINE STRESS ECHOCARDIOGRAPHY.

STUDY	REF	SELECTION	PROTOCOL	CRITERIA OF +
Sawada	17	*risk *chest pain *known CAD	up to 30 every 3'	< wall thickening or wall motion compared with the previous stage (Digital)
Cohen	18	chest pain	up to 40 every 3'	new WMA not present at baseline (Digital)
Previtali	19	Chest pain	up to 40 every 5'	new or worsened WMA (Videotape)
Segar	20	No clinical data	up to 30 every 3'	a lack of increase in wall motion/thickening was considered abnormal (Digital)
Mazeika	21	Suspected CAD	up to 20 every 8'	new or worsening regional asynergy (Videotape)
Salustri	22	Chest pain	up to 40 every 3'	new or worswned WMA (Both)
Marcovitz	23	*chest pain *post MI *risk *others	up to 30	*normal=hyperdynamic wall motion during dobutamine infusion *ischemic = dyssynergy developed during dobutamine infusion (Both)
Marwick	25	Chest pain	up to 40 every 3'	lack of improvement and/or worsening of wall motion

TABLE V.

COMPARISON OF STRESS ECHOCARDIOGRAPHY AND EXERCISE ELECTROCARDIOGRAPHY FOR THE DETECTION OF CORONARY ARTERY DISEASE.

STUDY	REF	Nr	STRESS	ECHO Sens	ECHO Spec	ECG Sens	ECG Spec
Morganroth	2	32	SB	48	91	62	91
Maurer	3	36	TR	83	92	52	77
Limacher	4	40	TR	79	94	71	94
Armstrong	29	59	TR	80	87	59	89
Ryan	8	64	TR	78	100	60	50
Pozzoli	11	75	UB	71	96	55	81
Galanti	12	53	UB	93	96	78	65
Crouse	13	228	TR	97	64	51	62
Marwick	15	61	TR	84	87	58	74
Mazeika	21	36	DOB	65	100	65	69
Salustri	22	35	DOB	62	67	46	89
Picano	26	76	DIP	75	100	67	71
Masini	27	68	DIP	77	93	69	52
Total		863		76	90	61	74

SB = supine bicycle; UB = upright bicycle; TR = treadmill.

TABLE VI.

COMPARISON OF STRESS ECHOCARDIOGRAPHY AND NUCLEAR TECHNIQUES FOR THE DETECTION OF CORONARY ARTERY DISEASE.

				ECHO		NUCLEAR	
STUDY	REF	Nr	NUCLEAR	Sens	Spec	Sens	Spec
Limacher	4	41	RNV	92	88	71	82
Visser	5	35	RNV	76	92	91	100
Crawford	34	18	RNV	89	92	77	100
Wann	35	16	Th-EX	55	100	73	100
Maurer	3	36	Th-EX	83	92	74	92
Pozzoli	11	75	MIBI-EX	71	96	84	88
Salustri	36	30	MIBI/Th-EX	76	85	82	69
Galanti	12	53	Th-EX	93	96	100	92
Quinones	14	112	Th-EX	74	88	76	81
Forster	24	21	MIBI-DOB	75	89	83	89
Marwick	25	97	MIBI-DOB	85	82	80	74
Totale		534		79	91	81	88

RNV = radionuclide ventriculography.

SUMMARY

Transient wall motion abnormalities are a very specific sign of myocardial ischaemia. Technical improvements in cardiac ultrasound systems provide the basis for detection of such abnormalities by two-dimensional exhocardiography.

This study is based on the results of application of different stress modalities with echocardiography in different clinical conditions. These are compared with those obtained with myocardial scintigraphy, the traditional method for detecting myocardial ischaemia. The studies in this thesis are divided into four parts. The first is an introduction on stress echocardiography, the second deals with exercise echocardiography, the third reports the results obtained with pharmacological stress echocardiography, and in the fourth a brief review of the state-of-the-art of this technique is given.

Chapter 1 presents a review of the pathophysiological basis of stress echocardiography, with a description of the echocardiographic signs of myocardial ischaemia. The different types of stress commonly used are described, with the protocols used at the Thoraxcenter of the University Hospital in Rotterdam. The application of digital system acquisition of images is outlined. Finally, the differences between stress echocardiography and myocardial perfusion scintigraphy are discussed, along with practical advantages of each method.

The application of exercise echocardiography in clinical practice and the comparison with myocardial scintigraphy are reported in Part Two. Exercise echocardiography proved to be a feasible test for the non-invasive diagnosis of myocardial ischaemia, with a good overall agreement with myocardial scintigraphy (chapter 2). However, there was a trend for a higher prevalence of transient perfusion defects when ischaemia occurred in the inferior or posterolateral areas, or in patients with previous myocardial infarction. In a group of 75 patients with normal ECG at rest (chapter 3), sensitivity and specificity of exercise echocardiography for the diagnosis of coronary artery disease were 71% and 96%, respectively, similar to those obtained with myocardial scintigraphy.

In order to clarify these preliminary findings, we evaluated with the same modalities patients with isolated single-vessel stenoses of different

severity evaluated by caliper (chapters 4 and 5). A delay in recording echocardiographic images lowered the potential value of exercise echocardiography. SPECT detected more patients with "ischaemia", expecially when stenoses of intermediate severity were present.

As a consequence of these encouraging results, exercise echocardiography was applied for evaluating patients prior to percutaneous transluminal coronary angioplasty. The results of this study, reported in Chapter 6, confirm that exercise echocardiography compares favourably with SPECT imaging, and is particularly suitable for the assessment of the functional results of revascularization procedures with PTCA.

Finally, a general review on the comparison between exercise echocardiography and SPECT is reported in Chapter 7.

The value of dobutamine stress echocardiography in clinical practice is reported in Chapter 8. The test is feasible and safe, with a sensitivity and specificity for detection of coronary artery disease (with quantitative measurements of coronary artery diameter) of 54% and 80%, respectively. Despite this suboptimal value of sensitivity, dobutamine stress echocardiography showed a favourable trend in comparison with exercise electrocardiography, expecially in patients with single-vessel disease.

The results of a direct comparison between dobutamine and dipyridamole as stress agents are reported in Chapter 9. Despite the different mechanism of action, dobutamine and dipyridamole stress echocardiography showed similar results in terms of diagnostic accuracy and side effects.

The results of combined echo/SPECT studies in 105 patients during dobutamine stress test are discussed in Chapter 10. There was a good agreement between the two techniques, both for the final diagnosis of myocardial ischaemia and for the regional analysis. The agreement was higher in patients without previous myocardial infarction.

Finally, the value of dipyridamole stress echocardiography for risk stratification after uncomplicated myocardial infarction is discussed in Chapter 11. In this clinical setting, reversible perfusion defects were more frequent than transient wall motion abnormalities, perhaps reflecting flow heterogeneity without true ischaemia. However, the prognostic information that we obtained were disappointing.

The informations from this study suggest that stress echocardiography is a versatile technique for non-invasive evaluation of coronary artery disease and myocardial ischaemia. It offers some clear advantages on myocardial scintigraphy, and therefore it should be preferred in most clinical conditions.

SAMENVATTING

Tijdelijke wand beweging stoornissen van het hart zijn kenmerkend voor ischemie. Vooruitgang van de echografische techniek heeft de basis gelegd voor het opsporen van deze afwijkingen door middel van twee-dimensionale echocardiografie.

Deze studie is gebaseerd op de resultaten van stress echocardiografie in verschillende klinische omstandigheden. Tevens worden de resultaten van stress echocardiografie vergeleken met hart scintygrafie, een meer gangbare nucleaire methode voor het opsporen van hart ischemie. De studie is onderverdeeld in vier hoofdstukken. Het eerste hoofdstuk is een inleiding over stress echocardiografie, het tweede behandeld inspanning echocardiografie, het derde de resultaten verkregen met medicamenteuze geinduceerde stress en echografische beoordeling van het hart en het vierde hoofdstuk is een overzicht van de huidige stand van zaken van deze nieuwe techniek.

Hoofdstuk 1 is een overzicht van de pathofysiologie van stress echocardiografie, met een omschrijving van de echografische kenmerken van het ischemische hart. De verschillende methoden om stress te induceren die in het Thoraxcentrum van de Erasmus Universiteit gangbaar zijn, worden beschreven. De toepassing van het "digital" systeem voor het verkrijgen van afbeeldingen wordt toegelicht. Ten slotte zullen de verschillen tussen stress echocardiografie en hart perfussie scintygrafie worden besproken met hun praktische toepassing.

Het toepassen van inspanning echocardiografie in de klinische praktijk en de vergelijking met hart scintygrafie wordt besproken in hoofdstuk 2. Inspanning echocardiografie is een goed uitvoerbare niet invasieve techniek om hart ischemie te detecteren, vergelijkbaar met hart scintygrafie. Perfussie scintygrafie van het hart toont vaker tijdelijke defecten aan als uiting van ischemie in het inferior en posterior-lateraal gedeelte van het hart, of in gebieden met een oud hart infarct.

In een groep van 75 patienten met een normaal ECG in rust (hoofdstuk 3) de sensitiviteit en specificiteit van inspanning echocardiografie voor de diagnose van coronair lijden was 71% en 96%, gelijkwaardig aan hart scintygrafie. Ten einde hier in duidelijkheid te brengen, werden beide onderzoek mogelijkheden toegepast bij patienten met een geisoleerde een taks vaatlijden met een stenose van wisselend kaliber, vast gesteld door de caliper (hoosdstuk 4 en 5). Een vertraging van de echografische opname na inspanning verminderd de diagnostische waarde van dit onderzoek. Spect detecteerde meer patienten met hart ischemie, met name wanneer er een matig ernstige stenose aanwezig was.

Als gevolg van deze veel belovende resultaten, werd inspanning echocardiografie toegepast bij patienten waar voor een PTCA procedure was afgesproken. De resultaten van deze studie worden gepresenteerd in hoofdstuk 6, en bevestigen dat inspanning echocardiografie gunstig afsteekt met SPECT, en is voor al geschikt voor het evalueren van het functionele resultaat van een PTCA procedure.

Ten slotte wordt een algemeen overzicht gegeven over de vergelijking tussen echocardiografie en SPECT in hoofdstuk 7.

De waarde van dobutamine stress echocardiografie in de dagelijkse praktijk wordt beschreven in hoofdstuk 8. De test is goed uitvoerbaar en veilig, met een sensitiviteit en specificiteit voor coronair lijden van 54% en respectievelijk 80%. De niet optimale sensitivitiet waarde kan verschillende redenen hebben, waarbij de voornaamste het gebruik van betablocker medicatie is als anti-angineuze medicatie die echter ook een antagonist van dobutamine is. In vergelijking met inspanning echocardiografie lijkt dobutamine stress echocardiografie een beter diagnostische waarde te hebben voor coronair lijden, vooral in patienten met een taks coronair lijden.

Een vergelijking tussen deze twee medicijnen in dezelfde patienten wordt gepresenteerd in hoofdstuk 9. Hoewel deze medicijnen een verschillend werking mechanisme hebben, vertonen dobutamine en dipyridamole stress echocardiografie een zelfde diagnostische waarde en bijwerkingen.

De resultaten van gecombineerde echocardiografie/SPECT onderzoeken in 105 patienten onder dobutamine stress worden beschreven in hoofdstuck 10. Er is een goede overeenkomst tussen beide techieken, zowel voor de diagnose van hart ischemie als voor regionale afwijkingen. De overeenkomst was beter in patienten die een hart infarct hadden door gemaakt.

De waarde van dipyridamole stress echocardiografie voor risico stratificatie na een hart infarct wordt beschreven in hoofdstuk 11. In deze patienten groep komen tijdelijke perfussie stoornissen vaker voor dan tijdelijke wand beweging stoornissen, mogelijk veroorzaakt door redistributie van bloed dan werkelijke ischemie. De prognostische waarde van deze bevindingen wordt tevens vermeldt. De informatie van deze studie suggereert dat stress echocardiografie een veel belovende niet invasieve techniek is voor de evaluatie van coronair lijden en myocard ischemie. Het heeft duidelijke voordelen op myocard scintygrafie en zou derhalve de voorkeur moeten hebben in de meeste omstandigheden.

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